Chapter 3: Risk

CHAPTER CONTENTS

CHAPTER OVERVIEW

This chapter presents the hazards, exposures, and associated health and environmental risks that may result from the chemicals in the solvent-based, water-based, and UV-cured ink systems studied in the CTSA.

INTRODUCTION TO RISK: Section 3.1 presents an introduction to the central concepts of risk. Common steps of a risk assessment are described, including hazard identification, dose-response assessment, exposure assessment, and risk characterization. Finally, three major types of potential effects of hazardous substances on living organisms (systemic toxicity, developmental toxicity, and carcinogenic effects) are described.

HAZARD IDENTIFICATION: Section 3.2 discusses the human health and ecological hazards of all the chemicals in the flexographic inks included in this study. The information is based on data found in published toxicological studies as well as reports prepared by the EPA Structure Activity Team (SAT). Detailed information can be found in Appendices 3-A and 3-B. Additionally, some chemicals are regulated under major federal regulations; information about the applicability of these regulations can be found in Chapter 2.

CHEMICAL CATEGORIES: Section 3.3 describes the chemical categories into which the flexographic ink chemicals were organized for this CTSA. Subsequent sections of the risk assessment discuss these chemical categories rather than specific chemicals, in order to protect the confidentiality of ink manufacturers regarding specific ink formulations. This section also identifies the relevant chemical categories for each of the ink formulations studied.

AIR RELEASES: Section 3.4 presents the environmental air releases that may result from using these flexographic inks. The results were generated with mass balance calculations.

EXPOSURE ASSESSMENT FOR WORKERS AND GENERAL POPULATION: Section 3.5 discusses the potential dermal and inhalation exposures to workers that can occur as a result of working with these inks. The exposure assessment was performed under two modeled scenarios: the ink preparation room (Scenario 1) and the press room (Scenario 2). The results of both scenarios are presented in this section, but only the results from Scenario 2, which yielded higher exposure rates, are used for the subsequent Risk Characterization. Section 3.6 presents potential inhalation exposures for the general population.

RISK CHARACTERIZATION: Lastly, Section 3.7 describes the risk characterization for these flexographic inks. The risk characterization integrates the hazard and exposure information to arrive at risk estimates to workers and the exposed general population near to a flexographic facility.

HIGHLIGHTS OF RESULTS

Useful information can be gleaned from each section of this chapter. However, when comparing the overall impacts of ink formulations, the risk characterization (Section 3.7) is the most relevant. These results are based on modeled assumptions about conditions and practices in flexographic printing facilities, and therefore may not represent all printing facilities. However, in any printing facility, workers are exposed to printing chemicals to some extent. Chapter 7 contains information about practices that can reduce or eliminate pollution and worker exposure from many steps in the printing process. Several of the important findings are noted on the next page.

- **Thirty of the 48 chemicals for which toxicological information is available were found to represent medium or high hazard levels for systemic or developmental toxic effects.** In addition, ethanol has been documented to be carcinogenic to humans. Another six chemicals show evidence of carcinogenicity via inhalation or dermal exposure routes, but are not classified as carcinogenic at this time. (See Section 3.2)
- With regard to **ecological hazard, the analysis found that 18 chemicals were of high concern, and another 35 had medium hazard rankings**. (See Section 3.2)
- **The solvent-based inks released considerably more volatile matter than the water-based and UV-cured inks.** Water-based and UV-cured ink releases were comparable; however, the UV-cured results should be interpreted as an upper limit or worst-case scenario, because in practice much of the volatile material reacts and becomes nonvolatile. (See Section 3.4)
- Inhalation exposure is related to air releases. **For workers in the press room, exposure is highest with solvent-based inks** because of their higher air release rate. For the general population, however, exposure from solvent-based inks is lower than that from water-based inks because of the anticipated use of emission control equipment with solvent-based inks.
- The dermal exposure for prep room and press room workers is comparable for all three ink systems, and there is no expected dermal exposure for the general population. (See Sections 3.5 and 3.6)
- **Each ink system contained chemicals of clear risk concern for occupational health.** For both solvent-based and water-based inks, the chemicals that most commonly were a clear concern for risk were solvents, with some colorants and other chemicals also listed. For UV-cured inks, chemicals of clear concern for occupational risk were monomers, pigments, additives, and some chemicals that crossed functional categories.
- **Regarding risk to the general population, no chemicals were found to be of clear concern.** Potential concern for risk was posed by some solvents in solvent-based and water-based inks, and by some monomers and other chemicals in UV-cured inks. (See Section 3.7)

CAVEATS

- These results analyze only 45 of the many thousands of ink formulations that are available. They represent only a snapshot taken at a small selection of printing facilities, and should not be taken as representative of inks in general.
- The results presented in this chapter were based on the ink formulations as submitted to DfE; reaction products or other changes in chemical composition resulting from the printing process (e.g., the curing process for UV-cured inks) were not considered.
- Information for some chemicals was incomplete. EPA's Structure Activity Team (SAT) estimated properties for these chemicals based on molecular structure, similarity to well-studied chemicals, and other factors, but SAT reports are less preferable than direct toxicological research results.
- The results of this analysis also are dependent on assumptions that may or may not be true for other printing situations. (The assumptions are stated in the chapter and accompanying appendices.) For example, dermal results were calculated based on the assumption that no gloves are worn. If workers wear gloves when working with these chemicals, dermal exposure and risk would be substantially lower than reported here. Readers are advised to use caution when applying any results from this analysis to other situations.
- The designation of a chemical as being of "high" hazard or "clear" concern for risk does not give any indication of the potency of a chemical other than the fact that it meets the defined minimum threshold. A chemical with a high hazard or clear concern for risk, therefore, may be slightly above the respective threshold, or may be far beyond that threshold.

3.1 INTRODUCTION TO RISK

This section describes common concepts and components of a risk assessment. This information provides a context in which to understand the risk assessment that was performed on the flexographic chemicals studied in this CTSA.

Background

Chemicals affect the health of humans and the environment in a variety of ways. Human exposure to chemicals may occur through air that is inhaled, through water and food that are ingested, or through skin contact. Exposure to particular chemicals may create concentration levels that result in cellular damage, which in turn may cause disease and death. A risk assessment is a four-step process that identifies chemicals that may present harm to humans and other organisms.

A risk assessment includes four primary parts:

1 hazard identification[a]
2 dose-response assessment
3 exposure assessment
4 risk characterization

Hazard Identification
The first step in a risk assessment is hazard identification. This asks whether a chemical *could* cause adverse health effects in humans or in nature. That is, have toxic or carcinogenic effects been observed in previous studies of the chemical? Hazard is independent of exposure, so it is necessary to conduct a dose-response assessment and exposure assessment before applying hazard information directly to a specific set of conditions.

Dose-response Assessment
A dose-response assessment determines the chemical's toxicity — the relationship between the dose of a chemical received and the incidence and severity of adverse health effects in the exposed population. Epidemiological or historical human-based data are the preferred sources used to determine toxicity values. If those types of data are not available, laboratory animal studies are evaluated to see how their data may apply to humans. Toxicity values are used to estimate effects resulting from exposure to a chemical.

In this CTSA, results of the hazard identification and dose-response assessment are presented together in one section.

Exposure Assessment
An exposure assessment identifies populations (e.g., different groups such as factory workers or residents of an area) that are or could be exposed to a chemical. The exposure assessment describes the population's composition and size, and it identifies the types, magnitudes, frequencies, and durations of their exposure to the chemical. For this project, the exposure assessment assumes that workers in a flexographic printing plant can be exposed to chemicals via dermal (skin) or inhalation (breathing) absorption, and that the general

[a]In Europe, hazard is referred to as "toxicity."

population can be exposed via inhalation only. It is assumed that neither population is subject to toxic effects via oral exposure (e.g., drinking or eating contaminated substances).

Risk Characterization

A risk characterization uses hazard, dose-response, and exposure information to develop quantitative and qualitative expressions of risk. A good risk characterization describes the assumptions, scientific judgments, and uncertainties embodied in the assessment.

Quantitative Expressions of Hazard and Risk

The manner in which estimates of hazard and risk are expressed depends on the nature of the hazard and the types of data upon which the assessment is based. For example, cancer risks are most often expressed as the probability of an individual developing cancer over a lifetime of exposure to the chemical in question. Risk estimates for adverse effects other than cancer are usually expressed as the ratio of the toxicological potency of the chemical to the estimated dose or exposure level received. A key distinction between cancer and other toxicological effects is that *most carcinogens are assumed to have no dose threshold*. That is, exposure to *any* amount of the chemical is assumed to carry some risk. Other toxicological effects are generally assumed to have a dose threshold — an exposure level below which a significant adverse effect is not expected.

The Reference Dose (RfD) is an estimate of the lowest daily human exposure that is likely to occur without appreciable risk of deleterious, non-cancerous effects during a lifetime. The RfD is usually expressed as an oral dose per kilogram of body weight (given in units of mg/kg/day). The Reference Concentration (RfC) is an analogous value for continuous inhalation exposure, usually expressed in mg/m^3 (milligrams per cubic meter).

Deriving an RfD or RfC involves determining a No Observed Adverse Effect Level (NOAEL) or Lowest Observed Adverse Effect Level (LOAEL) from an appropriate toxicological or epidemiological study, and then applying various uncertainty and modifying factors to arrive at the RfD or RfC. The NOAEL is the highest exposure level that can occur without statistically or biologically significant adverse effects, and the LOAEL is the lowest exposure level at which adverse effects have been shown to occur. Although some RfDs and RfCs are based on actual human data, they are most often calculated from results obtained in laboratory animal studies. The following represents the equation for a RfD:

$$\text{RfD} = \frac{\text{NOAEL (or LOAEL)}}{\text{UF} * \text{MF}} .$$

In this equation, the Uncertainty Factor (UF) reflects the various types of data sets used to estimate the RfD. For example, a valid chronic animal NOAEL is normally divided by a UF of 100. Several forms of uncertainty are accounted for in the UF: variation in sensitivity among members of the human population, the uncertainty in extrapolating animal data to the case of humans, the uncertainty in extrapolating from data obtained in a study that is of less-than-lifetime exposure, and the uncertainty in using LOAEL data rather than NOAEL data. The Modifying Factor (MF) is applied based on a professional judgment of the quality of the data available for the chemical. The default value for MF is 1.

Definitions of Systemic Toxicity, Developmental Toxicity, and Carcinogenic Effects

This risk assessment identifies systemic toxicity, developmental toxicity, and carcinogenic risks of chemicals found in the ink formulations used in the performance demonstrations. These measures are explained in more detail below.

Systemic Toxicity

Systemic toxicity refers to adverse effects on any organ system following absorption and distribution of a chemical throughout the body. *Adverse effects other than cancer and gene mutations are generally assumed to have a dose or exposure threshold*. Thus, much of the evaluation for systemic toxicity for each chemical will depend on the relationship between the threshold and the anticipated exposure.

RfDs and RfCs can be used to evaluate risks from chronic (long-term) exposures to systemic toxicants. EPA has defined an expression of risk called a Hazard Quotient (HQ), which is the ratio of the average daily dose to the RfD or RfC. HQ values below 1 imply that adverse effects are very unlikely to occur. The more the HQ exceeds 1, the greater the level of concern. It is important to remember that the HQ is not a probabilistic statement of risk; a quotient of 0.001 does not mean that there is a one-in-a-thousand chance of the effect occurring. Furthermore, it is important to remember that the level of concern does not necessarily increase linearly as the HQ approaches or exceeds 1. The HQ is calculated by the following equation:

$$HQ = \frac{ADD}{RfD\ (or\ RfC)}.$$

The derivation of the Average Daily Dose (ADD) is described in Section 3.7, Risk Characterization.

When an RfD or RfC is not available, risk may be expressed as the Margin of Exposure (MOE) instead of a HQ. The MOE is the ratio of a NOAEL or LOAEL (preferably from a chronic study) to an estimated dose or exposure level. The following equation represents the calculation of a MOE:

$$MOE = \frac{NOAEL\ (or\ LOAEL)}{calculated\ or\ measured\ human\ dose}.$$

High MOE values (e.g., greater than 100 for a NOAEL-based MOE or 1,000 for a LOAEL-based MOE) imply a low level of risk. As the MOE decreases, the level of risk increases. As with the HQ, it is important to remember that the MOE is not a probabilistic statement of risk.

Reproductive toxicity is also an important aspect of systemic toxicity. For purposes of this assessment, toxicity information on adult male and female reproductive systems was assessed.

Developmental Toxicity

EPA defines developmental toxicity as adverse effects on a developing organism that may result from exposure prior to conception, during prenatal development, or postnatally up to the time of sexual maturation. This is different from reproductive toxicity, which is a component of systemic toxicity and represents adverse effects on the reproductive systems of mature organisms. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity are (a) death, (b) structural abnormality, (c) altered growth, or (d) functional deficiency.

Because many elements associated with the hazard and exposure components of developmental toxicity risk assessment are unique, this assessment treats these risks separately from other systemic toxicity risks.

Developmental toxicity assessments usually assume that a single exposure at any developmental stage may be sufficient to produce an adverse developmental effect. In the case of intermittent exposures, an examination of the peak exposure(s) is as important as the average dose over the time period of exposure. In this project, however, an acute (short-term) risk sampling showed an insignificant likelihood of acute effects; therefore, further peak exposure modeling was not performed, and only average exposure values are presented in this report.

EPA has derived RfDs and RfCs for developmental toxicants in a manner similar to its derivation of RfDs and RfCs for systemic toxicants. The RfD_{DT} or RfC_{DT} is an estimate of a daily exposure to developmental toxicants by a human population that is assumed to be without appreciable risk of deleterious developmental effects. The use of the subscript "$_{DT}$" refers specifically to developmental toxicity.

Developmental toxicity risk can be expressed as a Hazard Quotient (dose or exposure level divided by the RfD_{DT} or RfC_{DT}) or a Margin of Exposure (NOAEL or LOAEL divided by the dose or exposure level).

Carcinogenic Effects

Carcinogenic effects are malignant tumors caused by cancer. EPA groups chemicals into one of the five weight-of-evidence categories, which indicate the extent to which the available data support the hypothesis that a substance causes cancer in humans. The categories are listed below:

- Group A — human carcinogen
- Group B — probable human carcinogen (B1 indicates limited human evidence, B2 indicates sufficient evidence in animals but inadequate or no evidence in humans)
- Group C — possible human carcinogen
- Group D — not classifiable as to human carcinogenicity
- Group E — evidence of noncarcinogenicity for humans

The International Agency for Research on Cancer (IARC) has an analogous categorization system; in this CTSA, both categorization systems are used wherever information is available.

The 1996 EPA proposed guidelines for carcinogenicity assessment use three categories to describe human carcinogenic potential:

- Known/Likely — available tumor effects and other key data are adequate to demonstrate carcinogenic potential for humans convincingly
- Cannot Be Determined — available tumor effects or other key data are suggestive, conflicting, or limited in quantity, and therefore are not adequate to demonstrate carcinogenic potential for humans convincingly
- Not Likely — experimental evidence is satisfactory for deciding that there is no basis for human hazard concern

When the available data are sufficient, EPA calculates a quantitative estimate of the chemical's carcinogenic potency. Three measures are the slope factor, unit risk, and cancer risk.

- **Slope factors** express carcinogenic potency in terms of the estimated upper-bound incremental lifetime risk, in milligrams per kilogram of body weight (mg/kg) average daily dose.

- **Unit risk** is a similar measure of potency for air or drinking water concentrations. Unit risk is expressed as risk per $\mu g/m^3$ (micrograms per cubic meter) in air or as risk per $\mu g/L$ (micrograms per liter) in water for continuous lifetime exposures.[b]

- **Cancer risk** is calculated by multiplying the estimated dose or exposure level by the appropriate measure of carcinogenic potency. For example, an individual who has a lifetime average daily dose of 0.003 mg/kg of a carcinogen with a potency of 0.02 mg/kg/day would experience a lifetime cancer risk of 0.00006 (1 in 17,000) from exposure to that chemical. In general, risks from exposure to more than one carcinogen are assumed to be additive (the risk caused by each additional chemical leads to a larger overall risk), unless other information points toward a different interpretation.

Definition of Aquatic Toxicity

Aquatic toxicity refers to an adverse effect on an aquatic organism following exposure to a toxicant. For this analysis, acute and chronic aquatic toxicity values were gathered for fish, aquatic invertebrates, and green algae. The acute values are reported in either of two ways:

- LC_{50}, the concentration at which 50 percent of test organisms die within a specified short-term exposure period
- EC_{50}, the concentration at which 50 percent of the organisms show an adverse (non-lethal) effect, such as growth inhibition, at the end of the exposure period.

[b] Sufficient input data were not available for the flexographic ink chemicals considered in this CTSA; therefore, slope factors or unit risk measures were not calculated for this analysis.

3.2 HUMAN HEALTH AND ECOLOGICAL HAZARDS

Human Health Hazards

Human Health Hazard Methodology

As a first step toward determining the hazards and potential exposure associated with each chemical found in the flexographic inks used in this study, EPA compiled information about their chemical and physical properties. Profiles of the CTSA chemicals are presented in Appendix 3-A. The profiles include the chemical structure and key properties, including molecular weight, melting and boiling point, vapor pressure, flash point, water solubility, density, and function in ink. The chemicals are listed alphabetically, with their synonyms and CAS numbers, in Table 3-A.1 of that Appendix.

Databases exist that list chemical hazard information used to characterize systemic, developmental, and carcinogenic effects. Most databases are available through online searching and are maintained by a variety of government and private organizations. They may contain both numeric and textual information relating to the chemicals. Some of the hazard databases used in the initial literature search for this CTSA include the following:

- EPA's Integrated Risk Information System (IRIS)
- National Library of Medicine's Hazardous Substances Data Bank (HSDB)
- TOXLINE
- TOXLIT
- GENETOX
- Registry of Toxic Effects of Chemical Substances (RTECS)
- American Conference of Governmental Industrial Hygienists (ACGIH)
- Agency for Toxic Substances and Disease Registry (ATSDR)
- National Toxicology Program (NTP)
- International Agency for Research on Cancer (IARC)
- National Institute for Occupational Safety and Health (NIOSH)
- Occupational Safety and Health Administration (OSHA)

These databases yielded secondary data for this report; no attempts were made to verify the information. Other data were also reviewed, including toxicological data developed under EPA's Office of Pollution Prevention and Toxics' Chemical Testing Program, as well as unpublished data submitted under TSCA §§ 8(d) and 8(e) found in the TSCA Test Submissions System and TRIAGE databases.

Human health hazard profiles were prepared for chemicals about which human toxicological data exist in databases. A hazard level (low, medium, or high) was assigned to each chemical based on the available data for dermal and inhalation routes for systemic and developmental effects.

When toxicity data were not available for particular exposure routes, toxicity values were estimated based on data from other exposure routes. For example, the systemic LOAEL (dermal exposure route) for ammonia was derived from oral exposure data. In addition, some data originating from an inhalation study, for example, may have been systematically converted to oral toxicity value before being converted back to an inhalation value for this analysis. In general, using toxicity values derived from alternate pathway data increases the uncertainty of the risk results.

Many of the chemicals contained in the flexographic inks researched in this CTSA were not represented adequately in the databases listed above. These chemicals were evaluated by the Structure Activity Team (SAT) of EPA's Office of Pollution Prevention and Toxics. The SAT provided hazard levels based on analog data and/or structure activity considerations, in which characteristics of the chemicals were estimated in part based on similarities with chemicals that have been studied more thoroughly. Using SAT hazard evaluations introduces a greater level of uncertainty in the results. SAT-based systemic toxicity concerns were ranked according to the following criteria:

- **High concern** — evidence of adverse effects in humans, or conclusive evidence of severe effects in animal studies
- **Moderate concern** — suggestive evidence of toxic effects in animals; or close structural, functional, and/or mechanistic analogy to chemicals with known toxicity
- **Low concern** — chemicals not meeting the above criteria

When a chemical did not clearly fit one of the SAT concern level categories, ratings of low-moderate or moderate-high were assigned. It should be noted that SAT-based developmental toxicity concerns were not ranked; the SAT only indicated whether a concern for developmental toxicity existed for a given chemical.

Human Health Hazard Results

Tables 3.1 A-F present a summary of the hazard information for each chemical used in this CTSA. The tables contain the following columns.

- **Chemical Category** indicates the category under which the chemical is grouped. These categories are the basis of the subsequent release, exposure, and risk analyses.
- **Ink System** lists the ink systems that contain at least one chemical within each chemical category.
- **Chemical/CAS#** presents the name of the chemical and the Chemical Abstracts Service (CAS) registry number assigned to the chemical.
- **Expected Exposure Route** indicates whether the data presented in subsequent columns is based on inhalation or dermal exposure. If inhalation exposure is not provided for a chemical, that indicates that the compound has a vapor pressure below 0.01 mm Hg, and therefore inhalation would not be expected.
- **Estimated Concentration of Concern** is a calculated figure based on toxicological data; it indicates the concentration at which systemic or developmental effects may begin to appear.
- **Concern for Toxic Effects** indicates whether the chemical poses a low, medium, or high hazard concern (see "Systemic Toxicological Effects" and "Developmental Toxic Effects" in this section for more information). There are two values presented in each cell: the first indicates the hazard level for systemic effects, and the second lists the hazard for developmental effects. An indication of whether the hazard level is based on toxicological data (Tox) or on a SAT report (SAT) follows in parentheses.
- **Toxicological Endpoints** presents the type of anticipated health effects that have been reported for animal or human studies. This is a qualitative listing of reported effects; it does not imply anything about the severity of the effects or the doses at which the effects occur.

This section describes the overall hazard findings and then presents a summary for each ink function (e.g., solvents and colorants). For a more detailed presentation of health hazard results, see Tables 3-B.1 and 3-B.2 in Appendix 3-B.

Hazard is summarized for systemic and developmental effects. For chemicals with toxicological data, a level of low, medium, or high are assigned based on the available dose-response information.

Systemic Toxic Effects: Hazard levels for systemic toxic effects of the flexographic ink chemicals were derived from subchronic/chronic toxicity information found in the human health hazard profiles (see Appendix 3-B).[3] The following results are shown in Table 3.1:

- Twenty-one chemicals presented a low hazard (practically non-toxic to slightly toxic, dermal $LD_{50} > 2$ g/kg).[c]
- Twenty presented a medium hazard (moderately toxic at subchronic/chronic oral doses > 50 mg/kg).
- One, ethanol, presented a high hazard (severe to frank toxicity at subchronic/chronic oral doses ≤ 50 mg/kg).

The most common systemic effects observed in animal studies are listed below. Toxic effects seen in animals were presumed to be also manifested in humans.

- respiratory and neurotoxic effects (19 chemicals)
- altered organ weights (19 chemicals)
- liver effects (18 chemicals)
- blood effects (15 chemicals)
- decreased body weight or body weight gain (15 chemicals)
- reproductive effects (14 chemicals)
- kidney effects (12 chemicals)
- changes in serum or clinical chemistry (nine chemicals)
- skin effects (eight chemicals)

Chemicals without adequate systemic toxicity data were evaluated by the SAT. The SAT reports indicated that 14 chemicals were of low hazard, 35 were of low to moderate hazard, and four were of moderate hazard.[4] None were of high hazard.

Developmental Toxic Effects: Adequate developmental toxicity data (including NOAELs or LOAELs) were available for 24 flexographic ink chemicals. RfD_{DT} and RfC_{DT} were not available for any of the chemicals. Hazard levels for developmental effects of these chemicals were derived from developmental toxicity information found in the human health hazard profiles.[5] The following are shown in Table 3.1:

- Sixteen chemicals presented a low hazard (no effects or effects seen at oral doses >250 mg/kg/day).
- Four presented a medium hazard (effects seen at oral doses of 50 to 250 mg/kg/day).
- Four (barium, ethanolamine, isopropanol, and styrene) presented a high hazard (effects seen at oral doses ≤50 mg/kg/day).

The most common developmental effects observed in animal studies are listed below. Toxic effects seen in animals were presumed to be also manifested in humans.

[c] LD_{50} is the dose of a chemical taken by mouth, adsorbed by the skin, or injected that is estimated to cause death in 50 percent of the test animals.

- decreased pre- or post-natal survival and decreased fetal body weight or body weight gain (nine chemicals)
- fetal malformations (seven chemicals)
- retarded skeletal and/or muscle growth and development (four chemicals)
- inhibited or altered fetal growth and/or development (three chemicals)
- delayed, poor, or non-ossification of bones (three chemicals)
- altered fetal organ weights (three chemicals)
- central nervous system structural anomalies (two chemicals)
- altered gonad growth and development (two chemicals)
- skeletal variants (three chemicals)
- unspecified fetotoxicity (two chemicals)

Of the chemicals without adequate developmental toxicity data, SAT reports indicated a developmental hazard for 15 chemicals.

Table 3.1 lists each chemical used in the study and is separated into six sections; each table corresponds to the chemicals' function in the ink. Basic definitions of each function can be found in Chapter 2.

Solvents (Table 3.1-A): Sixteen of the chemicals studied in this CTSA are categorized as solvents. Nearly all are volatile, and therefore can be inhaled. Twelve of them have toxicological data; the remaining four were studied by the SAT. As indicated in Table 3.1-A, propylene glycol ethers generally had the lowest hazard rankings, and ethylene glycol ethers and alcohols had the highest rankings.

Colorants (Table 3.1-B): Seventeen chemicals were colorants. In this CTSA, all of the colorants used were pigments, or dispersed solid particles. Few of the chemicals have undergone toxicological testing, so most (all but five) were analyzed by the SAT. Because the compounds are solids with essentially no vapor pressure, none were expected to result in inhalation exposure. Table 3.1-B presents the hazard information on the colorants; most present a low-moderate dermal hazard as determined by the SAT.

Resins (Table 3.1-C): Ten chemicals in this CTSA were classified as resins. Eight were analyzed by the SAT, and one (miscellaneous resins) could not be studied because there was not enough information to perform a SAT analysis. Toxicological data were available for one chemical. As shown in Table 3.1-C, most chemicals have a low hazard.

Additives (Table 3.1-D): Twenty one chemicals were categorized as additives. Toxicological data were available for five chemicals, and the SAT analyzed 12 others. There was not enough information available for the SAT to analyze four chemicals. Table 3.1-D indicates that the organotitanium compounds were the category with most concern, with all chemicals in that category having a medium hazard level according to the SAT.

UV-Reactive Compounds (Table 3.1-E): Seventeen chemicals are included in this group. Table 3.1-E further groups these compounds according to three functions: monomers, oligomers, and photoinitiators. Toxicological data were available for five chemicals, and the SAT analyzed the remaining chemicals. Monomers were the most consistently hazardous chemicals — all had medium hazard concern for systemic toxic effects. However, two photoinitators and an oligomer also were found to have a medium hazard level.

Multiple-Function (Table 3.1-F): This group contains chemical categories for which the included chemicals are used in two or more ink functions. For example, the category *amides*

and nitrogenous compounds contains chemicals that are solvents or additives. Of the 18 chemicals in Table 3.1-F, toxicological data are available for 13, and the others were analyzed by the SAT. Six chemicals in this category have either medium or high hazard levels for toxic effects (either systemic or developmental).

Table 3.1-A Hazard Information for SOLVENTS Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Alcohols	Solvent Water UV	Ethanol 64-17-5	dermal	H/M (Tox)	endocrine, gastrointestinal, liver, reproductive, neurotoxic, pancreatic, rectal, heart, hormone, immune and developmental effects [c]
			inhalation	L/L(Tox)	blood, liver, spleen, thymus, bone marrow, neurotoxic, reproductive and developmental effects
		Isobutanol 78-83-1	dermal	L-M/NA (Tox)	neurotoxic effects
			inhalation	M/NA (Tox)	blood, enzyme, and neurotoxic effects
		Isopropanol 67-63-0	dermal	L-M/H (Tox)	blood, skin, and developmental effects, altered organ weights [c]
			Inhalation	M/L (Tox)	liver, neurotoxic, reproductive, respiratory, spleen and developmental effects, changes in enzymes, clinical, and urine chemistry
		Propanol 71-23-8	dermal	M/L (Tox)	liver, bone marrow and neurotoxic effects, altered organ weights [c]
			inhalation	M/L (Tox)	liver, reproductive, and developmental effects
		Tetramethyldecyndiol 126-86-3	dermal	L/NA (SAT)	concern for eye, skin, lung, and mucous membrane irritation, and neurotoxic, liver, and kidney effects
Alkyl acetates	Solvent	Butyl acetate 123-86-4	dermal	L/L (Tox)	changes in serum chemistry and blood pressure[c]
			inhalation	L/L (Tox)	changes in serum chemistry and blood pressure, developmental effects
		Ethyl acetate 141-78-6	dermal	L/NA (Tox)	neurotoxic and respiratory effects, mortality, altered body and organ weights [c]
			inhalation	M/NA (Tox)	blood, heart, gastrointestinal, kidney, liver, neurotoxic and respiratory effects, altered organ weights
		Propyl acetate 109-60-4	dermal	L-M/L-M (SAT)	Dermal LD50 > 20 mL/kg (species not indicated)
			inhalation	L-M/L-M (SAT)	

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-A Hazard Information for SOLVENTS Used in the Flexography CTSA (continued)

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Ethylene glycol ethers	Water	Alcohols, C11-15-secondary, ethoxylated, 68131-40-8	dermal	M/M (SAT)	lung effects, eye and severe skin irritation
			inhalation	M/M (SAT)	lung effects, eye and severe skin irritation
		Butyl carbitol 112-34-5	dermal	L/L (Tox)	blood and skin effects
			inhalation	M/L (Tox)	liver effects
		Ethoxylated tetramethyldecyndiol 9014-85-1	dermal	L-M/NA (SAT)	concern for eye, skin, lung, and mucous membrane irritation and neurotoxic, liver and kidney effects.
			inhalation	L-M/NA (SAT)	concern for eye, skin, lung, and mucous membrane irritation and neurotoxic, liver, kidney, and lung effects
		Ethyl carbitol 111-90-0	dermal	M-H/L (Tox)	bladder, blood, kidney, liver, neurotoxic, reproductive, spleen, and blood chemistry effects, altered organ weights [c]
			inhalation	M-H/L (Tox)	bladder, blood, kidney, liver, neurotoxic, reproductive, spleen, and blood chemistry effects, altered organ weights [c]
		Polyethylene glycol 25322-68-3	dermal	L/NA (Tox)	Not reported to be a dermal sensitizer based on studies with several materials.
			inhalation	L/NA (Tox)	
Propylene glycol ethers	Solvent Water	Dipropylene glycol methyl ether 34590-94-8	dermal	L/NA (Tox)	neurotoxic effects; not reported to be a dermal sensitizer in humans.
			inhalation	L/NA (Tox)	decreased growth, liver and neurotoxic effects, increased kidney weights
		Propylene glycol methyl ether 107-98-2	dermal	L/L (Tox)	increased mortality, blood, neurotoxic, and skin effects, altered organ weights
			inhalation	L/L (Tox)	decreased growth, liver, neurotoxic, reproductive, and respiratory effects, altered organ weights, and developmental effects
		Propylene glycol propyl ether 1569-01-3	dermal	M/L (Tox)	eye and neurotoxic effects, altered body and organ weights [c]
			inhalation	M/L (Tox)	eye and neurotoxic effects, altered body and organ weights

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-B Hazard Information for COLORANTS Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Pigments – Inorganic	Solvent Water UV	C.I. Pigment White 6 13463-67-7	dermal	L/NA (Tox)	bile duct, lymphatic, and respiratory effects [c]
		C.I. Pigment White 7 1314-98-3	dermal	L-M/L-M (SAT)	concern for mutagenicity, developmental toxicity, and immunotoxicity
Pigments – Organic	Solvent Water UV	C.I. Pigment Blue 61 1324-76-1	dermal	L/L (SAT)	low concern overall
		C.I. Pigment Red 23 6471-49-4	dermal	L/NA (Tox)	blood, kidney, and stomach effects [c]
		C.I. Pigment Red 269 67990-05-0	dermal	L/L (SAT)	low concern overall
		C.I. Pigment Violet 23 6358-30-1	dermal	L/L (SAT)	low concern overall
		C.I. Pigment Yellow 14 5468-75-7	dermal	L-M/L-M (SAT)	concern for oncogenicity, mutagenicity, neurotoxicity, and liver effects
		C.I. Pigment Yellow 74 6358-31-2	dermal	L/L (SAT)	low concern overall
Pigments – Organo-metallic	Solvent Water UV	C.I. Basic Violet 1, molybdatephosphate 67989-22-4	dermal	L-M/L-M (SAT)	concern for oncogenicity, mutagenicity, and developmental toxicity
		C.I. Basic Violet 1, molybdatetungstatephosphate 1325-82-2	dermal	L-M/L-M (SAT)	concern for oncogenicity, mutagenicity, developmental toxicity, immunosuppression, methemoglobinemia, and liver effects
		C.I. Pigment Blue 15 147-14-8	dermal	L/NA (Tox)	low or negligible concern
		C.I. Pigment Green 7 1328-53-6	dermal	L/NA (Tox)	altered body weight [c]
		C.I. Pigment Red 48, barium salt (1:1) 7585-41-3	dermal	L-M/NA (SAT)	concern for oncogenicity
		C.I. Pigment Red 48, calcium salt (1:1) 7023-61-2	dermal	L-M/NA (SAT)	concern for oncogenicity
		C.I. Pigment Red 52, calcium salt (1:1) 17852-99-2	dermal	L-M/L-M (SAT)	concern for mutagenicity, developmental toxicity, and oncogenicity
		C.I. Pigment Violet 27 12237-62-6	dermal	L-M/L-M (SAT)	concern for oncogenicity, mutagenicity, developmental toxicity, and neurotoxicity.
		D&C Red No. 7 5281-04-9	dermal	M/L (Tox)	thymus, reproductive, and kidney effects, altered organ weights and clinical chemistry

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-C Hazard Information for RESINS Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Polyol derivatives	Solvent UV	Nitrocellulose 9004-70-0	Dermal	L-M/L-M (SAT)	Oral LD_{50} in rats and mice >5 grams/kg. Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Polyol derivative A[c] CAS: NK	Dermal	L/L (SAT)	low concern overall
Resins	Solvent Water	Fatty acid, dimer-based polyamide CAS: NK	Dermal	L/L (SAT)	low concern overall
		Fatty acids, C 18-unsatd., dimers, polymers with ethylenediamine, hexamethylenediamine, and propionic acid 67989-30-4	Dermal	L/L (SAT)	low concern overall
		Resin acids, hydrogenated, methyl esters 8050-15-5	Dermal	L/L (SAT)	low concern overall
		Resin, acrylic CAS: NK	Dermal	L/L (Tox)	no effects
		Resin, miscellaneous CAS : NK		NA/NA	
		Rosin, fumarated, polymer with diethylene glycol and pentaerythritol 68152-50-1	Dermal	L/L (SAT)	Low concern overall unless respirable particles of high molecular weight species (>10,000) are inhaled. There is uncertain concern for respiratory sensitization.
		Rosin, fumarated, polymer with pentaerythritol, 2-propenoic acid, ethenyl benzene, and (1-methylethylenyl) benzene CAS: NK	Dermal	L/L (SAT)	
		Rosin, polymerized 65997-05-9	Dermal	L/L (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled. There is uncertain concern for respiratory sensitization.

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Actual name is confidential business information.

Table 3.1-D Hazard Information for ADDITIVES Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Acrylic acid polymers	Water	Acrylic acid-butyl acrylate-methyl methacrylate-styrene polymer 27306-39-4	Dermal	L/L (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Acrylic acid polymer, acidic (#1 and #2) CAS: NK	Dermal	L/NA (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Butyl acrylate-methacrylic acid-methyl methacrylate polymer 25035-69-2	Dermal	L/L (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Styrene acrylic acid polymer #1 CAS: NK	Dermal	NA/NA (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Styrene acrylic acid polymer #2 CAS: NK	Dermal	NA/NA (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Styrene acrylic acid resin CAS: NK	Dermal	NA/NA (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
Hydrocarbons – high molecular weight	Solvent Water	Distillates, petroleum, hydrotreated light 64742-47-8	Dermal	M/M (SAT)	concern for skin, eye, and mucous membrane irritation, carcinogenicity, genotoxicity, and narcosis at high doses; skin carcinogenicity (rats)
			Inhalation	M/M (SAT)	concern for skin, eye, and mucous membrane irritation, carcinogenicity, genotoxicity, and narcosis at high doses.
		Distillates, petroleum, solvent-refined light paraffinic 64741-89-5	Dermal	L/NA (Tox)	skin effects, benign skin tumors
			Inhalation	L/NA (Tox)	skin effects, benign skin tumors [c]
		Mineral oil 8012-95-1	Dermal	L/L (Tox)	oral study found low or negligible concern.
			Inhalation	L/L (Tox)	oral study found low or negligible concern.
		Paraffin wax 8002-74-2	Dermal	L-M/NA (SAT)	concern for respiratory effects
Olefin polymers	Water UV	Polyethylene 9002-88-4	Dermal	L/NA (SAT)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.
		Polytetrafluoroethylene 9002-84-0	Dermal	L/NA (Tox)	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-D Hazard Information for ADDITIVES Used in the Flexography CTSA (continued)

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Organic acids or salts	Solvent Water	Citric acid 77-92-9	Dermal	L/L (Tox)	oral study found low or negligible concern
		Dioctyl sulfosuccinate, sodium salt 577-11-7	Dermal	L-M/L-M (SAT)	developmental effects [c]
		Methylenedisalicylic acid 27496-82-8	Dermal	L-M/L-M (SAT)	concern for effects on blood clotting, sensitization, immunosuppression, irritation of mucous membranes, developmental toxicity, endocrine disruption, and genotoxicity
Organo-titanium compounds	Solvent	Isopropoxyethoxytitanium bis(acetylacetonate) 68586-02-7	Dermal	M/M (SAT)	concern for neurotoxicity, genotoxicity, oncotoxicity, and developmental/reproductive toxicity. This material is expected to be reactive which may result in irritation of the eyes, skin, and mucous membranes.
		Titanium diisopropoxide bis (2,4-pentanedionate) 17927-72-9	Dermal	M/M (SAT)	This compound is reactive, with moderate concern for eye, mucous membrane, and localized skin irritation. Hydrolysis products: concern for neurotoxicity, mutagenicity, oncogenicity, and developmental/reproductive toxicity (2,4-pentanedione); mutagenicity and oncogenicity (inorganic titanium); blood, liver, and skin effects, reproductive/developmental toxicity, and neurotoxicity (isopropanol)
		Titanium isopropoxide 546-68-9	Dermal	M/M (SAT)	This compound is reactive, with moderate concern for eye, mucous membrane, and localized skin irritation. Hydrolysis products: concern for mutagenicity and oncogenicity (inorganic titanium); blood, liver and skin effects, reproductive/developmental toxicity, and neurotoxicity (isopropanol)
Siloxanes	Solvent Water UV	Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica 68909-20-6	Dermal	L/L (SAT)	Low to moderate concern for lung effects (silicosis) if crystalline material is inhaled.
		Silicone oil 63148-62-9	Dermal	L/M (Tox)	reproductive and developmental effects
		Siloxanes and silicones, di-Me, 3-hydroxypropyl Me, ethers with polyethylene glycol acetate 70914-12-4	Dermal	NA/NA	Low to moderate concern for lung effects if respirable particles of high molecular weight species (>10,000) are inhaled.

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-E Hazard Information for UV-REACTIVE COMPOUNDS Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Monomers					
Acrylated polyols	UV	Dipropylene glycol diacrylate 57472-68-1	Dermal	M/M (SAT)	concern for genotoxicty, neurotoxicity, oncogenicity, developmental and reproductive effects, dermal and respiratory sensitization, and skin and eye irritation
			Inhalation	M/M (SAT)	concern for genotoxicty, neurotoxicity, oncogenicity, developmental and reproductive effects, dermal and respiratory sensitization, and skin and eye irritation
		1,6 Hexanediol diacrylate 13048-33-4	Dermal	M/L (SAT)	developmental effects [c]
			Inhalation	M/L (SAT)	developmental effects [c]
		Hydroxypropyl acrylate 25584-83-2	Dermal	M/NA (Tox)	respiratory effects [c]
			Inhalation	M/NA (Tox)	respiratory effects [c]
		Trimethylolpropane triacrylate 15625-89-5	Dermal	M/L (Tox)	skin and neurotoxic effects, altered organ and body weights, changes in clinical chemistry
Oligomers					
Acrylated polymers	UV	Acrylated epoxy polymer CAS: NK	Dermal	L-M/L-M (SAT)	If the polymer is terminated with acrylates, there is concern for mutagenicity, oncogenicity, developmental toxicity, and dermal sensitization.
		Acrylated oligoamine polymer CAS: NK	Dermal	L-M/L-M (SAT)	If the polymer is terminated with acrylates, there is concern for mutagenicity, oncogenicity, developmental toxicity, and dermal sensitization.
		Acrylated polyester polymer (#1 and #2) CAS: NK	Dermal	L-M/L-M (SAT)	If the polymer is terminated with acrylates, there is concern for mutagenicity, oncogenicity, developmental toxicity, and dermal sensitization.
		Glycerol propoxylate triacrylate 52408-84-1	Dermal	M/NA (Tox)	skin, neurotoxic, and respiratory effects, altered body weights
		Trimethylolpropane ethoxylate triacrylate 28961-43-5	Dermal	L-M/NA (SAT)	
		Trimethylolpropane propoxylate triacrylate 53879-54-2	Dermal	L-M/L-M (SAT)	concern for oncogenicity, mutagenicity, developmental and reproductive effects, sensitization, and irritation

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from a different exposure route.

Table 3.1-E Hazard Information for UV-REACTIVE COMPOUNDS Used in the Flexography CTSA (continued)

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Photoinitiators					
Aromatic ketones	UV	2-Benzyl-2-(dimethylamino)-4'-morpholinobutyrophenone 119313-12-1	Dermal	L/NA (Tox)	oral study found low or negligible concern
		2-Hydroxy-2-methylpropiophenone 7473-98-5	Dermal	M/NA (Tox)	liver effects, altered organ weights [c]
			Inhalation	M/NA (Tox)	liver effects, altered organ weights [c]
		1-Hydroxycyclohexyl phenyl ketone 947-19-3	Dermal	L/L (SAT)	low concern overall
		2-Isopropylthioxanthone 5495-84-1	Dermal	L/L (SAT)	low concern overall
		4-Isopropylthioxanthone 83846-86-0	Dermal	L/L (SAT)	low concern overall
		2-Methyl-4'-methylthio-2-morpholinopropiophenone 71868-10-5	Dermal	M/M (Tox)	blood, liver, eye, and neurotoxic effects, altered body weights [c]
		Thioxanthone derivative CAS NK	Dermal	L-M/NA (SAT)	concern for neurotoxicity

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from other exposure pathways.

Table 3.1-F Hazard Information for MULTIPLE-FUNCTION COMPOUNDS Used in the Flexography CTSA

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Amides or nitrogenous compounds	Solvent Water UV	Amides, tallow, hydrogenated 61790-31-6	Dermal	L/L (SAT)	low concern overall
		Ammonia 7664-41-7	Dermal	M/NA (Tox)	bone effects [c]
			Inhalation	L/NA (Tox)	corneal, liver, respiratory, and spleen effects
		Ammonium hydroxide 1336-21-6	Dermal	L/NA (Tox)	eye and respiratory effects [c]
			Inhalation	L/NA (Tox)	eye and respiratory effects
		Erucamide 112-84-5	Dermal	L/NA (SAT)	concern for myocardial effects
		Ethanolamine 141-43-5	Dermal	L/H (Tox)	developmental effects [c]
			Inhalation	L/H (Tox)	respiratory, kidney, liver, neurotoxic, and developmental effects [c]
		Hydroxylamine derivative CAS: NK	Dermal	M/M (SAT)	concern for genotoxicity, dermal sensitization, and developmental toxicity.
		Urea 57-13-6	Dermal	L/L (Tox)	not reported to be a dermal sensitizer
			Inhalation	L/L (Tox)	
Aromatic esters	UV	Dicyclohexyl phthalate 84-61-7	Dermal	L/L (Tox)	oral study found low or negligible concern.
			Inhalation	L/L (Tox)	oral study found low or negligible concern.
		Ethyl 4-dimethylaminobenzoate 10287-53-3	Dermal	L-M/L-M (SAT)	concern for genotoxicity, oncogenicity, neurotoxicity, cardiac sensitization, and developmental toxicity
			Inhalation	L-M/L-M (SAT)	concern for genotoxicity, oncogenicity, neurotoxicity, cardiac sensitization, and developmental toxicity

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from other exposure pathways.

Table 3.1-F Hazard Information for MULTIPLE-FUNCTION COMPOUNDS Used in the Flexography CTSA (continued)

Chemical Category	Ink System	Chemical/ CAS #	Expected Exposure Route[a]	Concern for Toxic Effects[b]	Toxicological endpoints and comments
Hydrocarbons—low molecular weight	Solvent Water	n-Heptane 142-82-5	Dermal	L/NA (Tox)	
			Inhalation	L/NA (Tox)	auditory and neurotoxic effects, altered serum chemistry
		Solvent naphtha, (petroleum), light aliphatic 64742-89-8	Dermal	L-M/NA (SAT)	concern for neurotoxicity and lung inhalation. This material may also cause defatting of the skin through prolonged exposure.
			Inhalation	L-M/NA (SAT)	concern for neurotoxicity and lung inhalation
		Styrene 100-42-5	Dermal	M-L/L (Tox)	
			Inhalation	M/H (Tox)	developmental effects
Inorganics	Solvent Water	Barium 7440-39-3	Dermal	M/H (Tox)	heart, kidney, reproductive, and developmental effects, altered organ weights, decreased survival [c]
		Kaolin 1332-58-7	Dermal	L/L (Tox)	respiratory effects, increased lung weight, lung carcinogenicity (rat), decreased pup body weight [c]
		Silica 7631-86-9	Dermal	NA/NA (Tox)	Concern for inhalation route.
Organophos-phorous compounds	Solvent UV	Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide 75980-60-8	Dermal	L/NA (Tox)	blood, reproductive, and skin effects, and altered body weights [c]
		2-Ethylhexl diphenyl phosphate 1241-94-7	Dermal	L-M/M (Tox)	liver, reproductive, spleen, and developmental effects, altered organ and body weights, changes in clinical chemistry [c]
		Phosphine oxide, bis(2,6-dimethoxybenzoyl)(2,4,4-trimethylpentyl)-, 145052-34-2	Dermal	M/NA (Tox)	neurotoxic, adrenal, blood, skin, enzyme, and liver effects, altered body weights, changes in serum chemistry [c]

[a] Inhalation hazard information was not included for compounds that are not expected to be volatile (i.e., that have a vapor pressure <0.001mmHg).
[b] The first letter(s) represents systemic concern; the second represents developmental concerns.
L= Low; M=Medium; H=High; NA=No data or information available
[c] Reported effects may have been observed from other exposure pathways.

Summary of Carcinogenic Information

The available information on the carcinogenic characteristics of chemicals in the flexographic inks studied is presented in Table 3.2. Quantitative data were not sufficient to calculate slope factors; therefore, the information in Table 3.2 is qualitative in nature.

Seven chemicals have been given classifications by either the International Agency for Research on Cancer (IARC) or EPA:

- Ethanol is an IARC Group 1 chemical, which indicates that there is sufficient evidence that it is carcinogenic to humans.
- Amorphous silica, isopropanol, polyethylene, and polytetrafluoroethylene are IARC Group 3 chemicals, which indicates that their characteristics with respect to cancer cannot be determined. The evidence of carcinogenicity in humans is inadequate, and in experimental animals it is inadequate or limited.
- Propanol has been categorized by EPA as a Group C chemical, or possible human carcinogen.

Six additional chemicals are listed for which evidence of carcinogenicity via inhalation or dermal exposure routes has been documented in literature, but which have not been assigned IARC or EPA classifications. Three of these chemicals, C.I. Pigment White 6, kaolin, and acrylic resin, have been documented to cause lung tumors in rats. Two types of petroleum distillates, hydrotreated light and solvent-refined light paraffinics, have been shown to cause skin tumors in mice. Styrene has been documented to cause mammary tumors in rats. It is important to note that because there are physiological differences between animals and humans, a chemical that produced evidence of carcinogenicity in animal studies will not necessarily be carcinogenic in humans. Conversely, because not all chemicals have been subjected to carcinogenicity studies, this list does not imply that chemicals not on the list are without concern.

SAT reports indicated low to moderate carcinogenicity hazard levels for 17 chemicals. All other chemicals for which SAT reports were generated indicated either low or negligible carcinogenicity hazard.

Table 3.2 Carcinogenicity Information for CTSA Chemicals

Chemical	Carcinogenicity Information
Ethanol	Classified as Group 1 by IARC: Inadequate evidence for carcinogenicity of ethanol and of alcoholic beverages in experimental animals, but sufficient evidence for carcinogenicity of alcoholic beverages in humans.
C.I. Pigment White 6	Evidence of lung tumors in rats.
Kaolin	
Resin, acrylic	
Distillates (petroleum), hydrotreated light	Evidence of skin tumors in mice.
Distillates (petroleum), solvent-refined light paraffinics	Evidence of benign skin tumors in mice.
Styrene	Evidence of mammary or breast tumors in rats.
Propanol	Classified as Group C by U.S. EPA: Possible human carcinogen, based on no evidence of carcinogenicity in humans and limited evidence of carcinogenicity in experimental animals.
Amorphous silica	Classified as Group 3 by IARC: Not classifiable as to its carcinogenicity to humans based on no or inadequate evidence in humans and experimental animals.
Isopropanol	
Polyethylene	
Polytetrafluoroethylene	
Acrylated epoxy polymer	These chemicals had no carcinogenicity study data, but SAT reports indicated low to moderate concern for carcinogenicity based on analogous structural, functional, and/or mechanistic data for chemicals with known carcinogenicity.
Acrylated oligoamine polymer	
Acrylated polyester polymer #1	
Acrylated polyester polymer #2	
C.I. Basic Violet 1, molybdatephosphate	
C.I. Basic Violet 1, molybdatetungstate-phosphate	
C.I. Pigment Red 48, barium salt (1:1)	
C.I. Pigment Red 48, calcium salt (1:1)	
C.I. Pigment Red 52, calcium salt (1:1)	
C.I. Pigment Violet 27	
C.I. Pigment Yellow 14	
Dipropylene glycol diacrylate	
Ethyl 4-dimethylaminobenzoate	
1,6-hexanediol diacrylate	
Isopropoxyethoxytitanium bis(acetylacetonate)	
Trimethylolpropane ethoxylate triacrylate	
Trimethylolpropane propoxylate triacrylate	

See "Definitions of Systemic Toxicity, Developmental Toxicity, and Carcinogenic Effects" in Section 3.1 for more information about cancer classifications.

Ecological Hazards

Ecological Hazard Methodology

This analysis addressed the ecological hazards of flexographic ink chemicals to aquatic species (fish, aquatic invertebrates, and green algae). Hazards to terrestrial species were not assessed because sufficient toxicity data were not available. Aquatic toxicity values may be obtained from the results of standard toxicity tests reported to EPA, published in the literature, or estimated using predictive techniques. Please see Appendix 3-B for more information about the methodology used in this analysis for determining ecological hazards.

For this study, discrete organic chemicals were assessed using predictive equations called Structure Activity Relationships (SARs), which estimate the acute and chronic toxicity of chemicals to aquatic organisms. The toxicity values relate to individual chemicals only; interactions among chemicals within a formulation were not considered. Although measured values are preferred, SAR estimates can be used in the absence of test data to estimate toxicity values within a specific chemical class. The equations are derived from correlation and linear regression analyses based on measured data.

Aquatic hazard profiles for each flexographic ink chemical consisted of a maximum of three acute toxicity values and three chronic values:

- Fish acute value (usually a fish 96-hour LC_{50} value)
- Aquatic invertebrate acute value (usually a daphnid 48-hour LC_{50} value)
- Green algal toxicity value (usually an algal 96-hour EC_{50} value)
- Fish chronic value (ChV) (usually a fish 28-day early life stage no-effect-concentration chronic value)
- Aquatic invertebrate chronic value (usually a daphnid 21-day ChV)
- Algal chronic value (usually an algal 96-hour value for biomass)

The ecological hazards of the chemicals were determined in a similar manner to the human hazards presented earlier in this section. The analysis was complicated by two issues: 1) many of the compounds were not addressed by existing aquatic toxicity test literature; and 2) some of the chemicals (e.g., petroleum-based products) were mixtures, not discrete compounds.

The concentration of concern was also derived for each chemical. This value was calculated by dividing the lowest of the three chronic values by a factor of ten. If the discharge of a chemical to the aquatic environment resulted in an estimated concentration equal to or greater than the concern concentration, then the chemical would likely be hazardous to organisms found in the aquatic environment.

For the purpose of an overall assessment, the listed chemicals can be given an aquatic hazard level according to the concentration of concern to obtain an estimated chronic value. A chronic value is the concentration of the chemical that results in no statistically significant sub-lethal effects on the test organism following a longer-term or chronic exposure. The hazard level is assigned according to the following criteria:

- High hazard chemicals: estimated chronic value $\leq$ 0.1 mg/L
- Medium hazard chemicals: 0.1 mg/L < estimated chronic value $\leq$ 10 mg/L
- Low hazard chemicals: estimated chronic value > 10 mg/L

Lower chronic values indicate higher hazard levels. For example, the presence of 0.1 mg of a high-hazard chemical in a liter of water could cause a problem, while at least 10 mg of a low-hazard chemical would have to be present to cause similar effects.

Ecological Hazard Limitations and Uncertainty

Some petroleum products, such as mineral spirits, petroleum distillates, and solvent naphtha, are mixtures. They do not lend themselves readily to the standard hazard assessment process using SARs, because the chemical constituents and the percentage of each in the mixture vary. The constituents in these products include linear and branched paraffins, and cyclic paraffins, with the total number of carbons ranging from five to sixteen.

For this CTSA, the toxicity of a mixture was determined by estimating the toxicity of each individual constituent. Lacking adequate description and characterization, it was assumed that each component was present in equal proportions in the product. The geometric mean of the range of estimates provided the best estimate of the toxicity. (These assumptions may not have been representative of the mixture currently on the market.) The toxicity of the individual components of the petroleum products was based on tests using pure samples. The potential byproducts or impurities of petroleum distillation that are typically found in these mixtures were not incorporated into this hazard assessment.

It was also not possible to estimate the hazard of some polymers, such as acrylic acid and polyamide polymers. However, these chemicals have molecular weights above 1,000 and structures that would make it difficult for them to be toxic to aquatic organisms. In general, nonionic polymers and those which are insoluble are of low aquatic hazard.

The aquatic hazard profiles for flexographic ink chemicals may consist of only measured data, only predicted values, or a combination of both, because data sources may be chemical-specific toxicity tests or SARs. Uncertainty or assessment factors were used to incorporate the concepts of uncertainty and variability into concern concentration calculations. These uncertainty factors include laboratory tests versus field data, measured versus estimated data, and differences in species' sensitivities. In general, if only one toxicity value is available, there is great uncertainty about the applicability of this value to other organisms in the environment. Conversely, when more information is available, there is more certainty about the toxicity values.

Ecological Hazard Results

The results of the estimated aquatic toxicity determinations are presented in Tables 3-B.3 and 3-B.4 in Appendix 3-B. The lowest or most sensitive values from SAR analysis or from actual measured test data were used. No valid, published literature was found to conflict with the estimated values. In many cases, the predicted and measured values were similar; for these chemicals, the lower value was selected for inclusion in Table 3-B.4. For each chemical, the estimated toxicity values are given in mg/L for acute and chronic effects to fish, daphnids, and algae. The last column lists the concern concentration set for the chemical in water.

For 26 chemicals, no aquatic toxic effects were expected, because the chemical structures are too large (molecular weight greater than 600 or 1,000) to pass through biological membranes. Nevertheless, concern concentrations were calculated whenever possible. Concern concentrations ranged from 0.001 to 20 mg/L.

All the chemicals then were ranked, based on the lowest of the three estimated chronic toxicity values. This relative toxicity ranking provides guidance to the selection and use of chemicals that are less hazardous to aquatic organisms. The chemicals with high and medium hazard rankings are summarized in Table 3.3. A more detailed presentation is provided in Table 3-B.4 in Appendix 3-B.

High hazard rankings were assigned to 18 chemicals. Thirty-five chemicals had medium hazard rankings. A low hazard rank was assigned to those chemicals for which a chronic value could not be calculated.

This study did not characterize risk for aquatic organisms, because routine water releases or discharges of hazardous chemicals were not anticipated from the use of the flexographic ink chemicals. Should such a release or discharge occur, the estimated or predicted environmental concentration would need to exceed the lowest chronic or acute toxicity value that was estimated for these chemicals to result in adverse effects.

However, all flexographic ink chemicals can theoretically be subject to accidental spills or releases. Also, many flexographic printing facilities routinely release wastewater to publicly owned water treatment plants (POTWs). Different geographic regions and different POTWs have different levels of acceptability for such wastes, and the acceptable levels can change over time. Discontinuing the use of chemicals that appear in Table 3.3 can help avoid potential problems.

Table 3.3 Chemicals of High and Medium Aquatic Toxicity (Based on Toxicological Studies)

18 Chemicals of high aquatic toxicity	
Amides, tallow, hydrogenated	Ammonia
C.I. Basic Violet 1, molybdatephosphate	C.I. Basic Violet 1, molybdatetungstatephosphate
C.I. Pigment Violet 27	Dicyclohexyl phthalate
Distillates (petroleum), hydrotreated light	2-Ethylhexyl diphenyl phosphate
Glycerol propoxylate triacrylate	n-Heptane
1,6-Hexanediol diacrylate	2-Isopropylthioxanthone
4-Isopropylthioxanthone	Mineral oil
Resin acids, hydrogenated, methyl esters	Styrene
Thioxanthone derivative	Trimethylolpropane ethoxylate triacrylate
35 Chemicals of medium aquatic toxicity	
Acrylic acid polymer, acidic #1	Acrylic acid polymer, acidic #2
Alcohols, C11-15-secondary, ethoxylated	Ammonium hydroxide
2-Benzyl-2-(dimethylamino)-4'-morpholinobutyrophenone	Butyl acetate
C.I. Pigment Blue 61	C.I. Pigment Red 48, barium salt (1:1)
C.I. Pigment Red 48, calcium salt (1:1)	C.I. Pigment Red 52, calcium salt (1:1)
Citric acid	D&C Red No.7
Dioctyl sulfosuccinate, sodium salt	Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide
Dipropylene glycol diacrylate	Ethanolamine
Ethyl acetate	Ethyl 4-dimethylaminobenzoate
1-Hydroxycyclohexyl phenyl ketone	Hydroxylamine derivative
Hydroxypropyl acrylate	Isopropoxyethoxytitanium bis(acetylacetonate)
Methylenedisalicylic acid	2-Methyl-4'(methylthio)-2-morpholinopropiophenone
Phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl)-	Propyl acetate
Resin, acrylic	Solvent naphtha (petroleum), light aliphatic
Styrene acrylic acid polymer #1	Styrene acrylic acid polymer #2
Styrene acrylic acid resin	Tetramethyldecyndiol
Titanium diisopropoxide bis (2,4-pentanedionate)	Trimethylolpropane propoxylate triacrylate
Trimethylolpropane triacrylate	

3.3 CATEGORIZATION OF FLEXOGRAPHIC INK CHEMICALS FOR THIS CTSA

This section describes the categories that each flexographic ink chemical was assigned for the purposes of the CTSA analysis. This was done because the specific chemical formulations of flexographic inks are generally considered to be proprietary. Manufacturers prefer not to reveal their formulations, because a competitor can potentially use this information to formulate and sell a nearly identical ink, often at a lower price without having to invest in research and development. Therefore, the Flexography Project developed a system to mask specific ink formulations discussed in the CTSA.

Each participating supplier voluntarily submitted a product line to EPA, where it was entered as Confidential Business Information (CBI). EPA completed the risk characterization using the exact formulations but without knowledge of the supplier. Each brand name was replaced with an ink system number (e.g., Solvent-based Ink #S1). This numbering system is used throughout the CTSA. In addition, to maintain the confidentiality of the formulations, the CTSA reports the results using the categorization system shown in Table 3.4. Results were reported for chemical categories only, and specific chemicals are not linked in the CTSA to any particular formulation. The final column in Table 3.4 presents the Chemical Abstracts Service (CAS) number for each chemical. Many chemicals have multiple names, so CAS numbers are used as a universal way of identifying unique chemicals.

In addition to the chemicals found in the flexographic ink formulations, press-side solvents and additives were used in most of the performance demonstration runs. Table 3-A.2 in Appendix 3-A lists the press-side solvents and additives used for each ink formulation at each demonstration site. These chemicals were also considered in this risk assessment.

Table 3.4 Categorization of Ink Chemicals

Category	Chemicals in category	CAS number
Acrylated polyols	Dipropylene glycol diacrylate	57472-68-1
	1,6-Hexanediol diacrylate	13048-33-4
	Hydroxypropyl acrylate	25584-83-2
	Trimethylolpropane triacrylate	15625-89-5
Acrylated polymers	Acrylated epoxy polymer[c]	NA[a]
	Acrylated oligoamine polymer[c]	NA
	Acrylated polyester polymer (#'s 1 and 2)[c]	NA
	Glycerol propoxylate triacrylate	52408-84-1
	Trimethylolpropane ethoxylate triacrylate	28961-43-5
	Trimethylolpropane propoxylate triacrylate	53879-54-2
Acrylic acid polymers	Acrylic acid-butyl acrylate-methyl methacrylate-styrene polymer	27306-39-4
	Acrylic acid polymer, acidic (#'s 1 and 2)[c]	NA
	Acrylic acid polymer, insoluble[c]	NA
	Butyl acrylate-methacrylic acid-methyl methacrylate polymer	25035-69-2
	Styrene acrylic acid polymer (#'s 1 and 2)[c]	NA
	Styrene acrylic acid resin[c]	NA
Alcohols	Ethanol	64-17-5
	Isobutanol	78-83-1
	Isopropanol	67-63-0
	Propanol	71-23-8
	Tetramethyldecyndiol	126-86-3
Alkyl acetates	Butyl acetate	123-86-4
	Ethyl acetate	141-78-6
	Propyl acetate	109-60-4
Amides or nitrogenous compounds	Amides, tallow, hydrogenated	61790-31-6
	Ammonia	7664-41-7
	Ammonium hydroxide	1336-21-6
	Erucamide	112-84-5
	Ethanolamine	141-43-5
	Hydroxylamine derivative	NA
	Urea	57-13-6
Aromatic esters	Dicyclohexyl phthalate	84-61-7
	Ethyl 4-dimethylaminobenzoate	10287-53-5
Aromatic ketones	2-Benzyl-2-(dimethylamino)-4'-morpholinobutyrophenone	119313-12-1
	1-Hydroxycyclohexyl phenyl ketone	947-19-3
	2-Hydroxy-2-methylpropiophenone	7473-98-5
	2-Isopropylthioxanthone	5495-84-1
	4-Isopropylthioxanthone	83846-86-0
	2-Methyl-4'-(methylthio)-2-morpholinopropiophenone	71868-10-5
	Thioxanthone derivative[c]	NA
Ethylene glycol ethers	Alcohols, C11-15-secondary, ethoxylated	68131-40-8
	Butyl carbitol	112-34-5
	Ethoxylated tetramethyldecyndiol	9014-85-1
	Ethyl carbitol	111-90-0
	Polyethylene glycol	25322-68-3

Table 3.4 Categorization of Ink Chemicals (continued)

Category	Chemicals in category	CAS number
Hydrocarbons — high molecular weight	Distillates (petroleum), hydrotreated light Distillates (petroleum), solvent-refined light paraffinic Mineral oil Paraffin wax	64742-47-8 64741-89-5 8012-95-1 8002-74-2
Hydrocarbons — low molecular weight	n-Heptane Solvent naphtha (petroleum), light aliphatic Styrene	142-82-5 64742-89-8 100-42-5
Inorganics	Barium Kaolin Silica	7440-39-3 1332-58-7 7631-86-9
Olefin polymers	Polyethylene Polytetrafluoroethylene	9002-88-4 9002-84-0
Organic acids or salts	Citric acid Dioctyl sulfosuccinate, sodium salt Methylenedisalicylic acid	77-92-9 577-11-7 27496-82-8
Organophosphorus compounds	Diphenyl (2,4,6-trimethylbenzoyl) phosphine oxide 2-Ethylhexyl diphenyl phosphate Phosphine oxide, bis(2,6-dimethoxybenzoyl) (2,4,4-trimethylpentyl)-	75980-60-8 1241-94-7 145052-34-2
Organotitanium compounds	Isopropoxyethoxytitanium bis(acetylacetonate) Titanium diisopropoxide bis(2,4-pentanedionate) Titanium isopropoxide	68586-02-7 17927-72-9 546-68-9
Pigments — inorganic	C.I. Pigment White 6 C.I. Pigment White 7	13463-67-7 1314-98-3
Pigments — organic	C.I. Pigment Blue 61 C.I. Pigment Red 23 C.I. Pigment Red 269 C.I. Pigment Violet 23 C.I. Pigment Yellow 14 C.I. Pigment Yellow 74	1324-76-1 6471-49-4 67990-05-0 6358-30-1 5468-75-7 6358-31-2
Pigments — organometallic	C.I. Basic Violet 1, molybdatephosphate C.I. Basic Violet 1, molybdate-tungstatephosphate C.I. Pigment Blue 15 C.I. Pigment Green 7 C.I. Pigment Red 48, barium salt (1:1) C.I. Pigment Red 48, calcium salt (1:1) C.I. Pigment Red 52, calcium salt (1:1) C.I. Pigment Violet 27 D&C Red No. 7	67989-22-4 1325-82-2 147-14-8 1328-53-6 7585-41-3 7023-61-2 17852-99-2 12237-62-6 5281-04-9
Polyol derivatives	Nitrocellulose Polyol derivative A[c]	9004-70-0 — [b]
Propylene glycol ethers	Dipropylene glycol methyl ether Propylene glycol methyl ether Propylene glycol propyl ether	34590-94-8 107-98-2 1569-01-3

Table 3.4 Categorization of Ink Chemicals (continued)

Category	Chemicals in category	CAS number
Resins	Fatty acid, dimer-based polyamide[c]	NA
	Fatty acids, C18-unsatd., dimers, polymers with ethylenediamine, hexamethylenediamine, and propionic acid	67989-30-4
	Resin acids, hydrogenated, methyl esters	8050-15-5
	Resin, acrylic[c]	NA
	Resin, miscellaneous[c]	NA
	Rosin, fumarated, polymer with diethylene glycol and pentaerythritol	68152-50-1 NA
	Rosin, fumarated, polymer with pentaerythritol, 2-propenoic acid, ethenylbenzene, and (1-methylethylenyl)benzene[c]	65997-05-9
	Rosin, polymerized	
Siloxanes	Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, hydrolysis products with silica	68909-20-6
	Silicone oil	63148-62-9
	Siloxanes and silicones, di-Me, 3-hydroxypropyl Me, ethers with polyethylene glycol acetate	70914-12-4

[a] No data or information available.
[b] Actual chemical name is confidential business information.
[c] Some structural information is given for these chemicals. For polymers, the submitter has supplied the number average molecular weight and degree of functionality. The physical property data are estimated from this information.

Chemical Categories by Product Line

This CTSA examined the health risks associated with two solvent-based, four water-based, and three UV-cured flexographic ink product lines run at 11 different performance demonstration sites. Tables 3.5, 3.6, and 3.7 list the chemical categories for each of these nine product lines. The categories are listed alphabetically. An "x" denotes that a chemical within that category is found at least once in the corresponding formulation.

Table 3.5 Categorization of Chemicals in Solvent-based Inks Used in the Performance Demonstrations

Chemical category	Solvent-based Ink #S1					Solvent-based Ink #S2				
	Blue	Green	White	Cyan	Magenta	Blue	Green	White	Cyan	Magenta
Alcohols	x	x	x	x	x	x	x	x	x	x
Alkyl acetates	x	x	x	x	x	x	x	x	x	x
Amides or nitrogenous compounds						x	x	x	x	x
Aromatic esters	x									
Hydrocarbons - high molecular weight			x							
Hydrocarbons - low molecular weight			x			x	x	x	x	x
Inorganics					x					
Organic acids or salts	x		x			x	x	x	x	x
Organophosphorous compounds						x	x		x	x
Organotitanium compounds	x		x							
Pigments - inorganic			x				x	x		
Pigments-organic		x					x			
Pigments-organometallic	x	x		x	x	x	x		x	x
Polyol derivatives	x	x	x	x	x	x	x		x	x
Propylene glycol ethers		x		x	x					
Resins	x	x	x	x	x	x	x	x	x	x
Siloxanes						x	x	x	x	x

Table 3.6 Categorization of Chemicals in Water-based Inks Used in the Performance Demonstrations

Chemical category	Water-based Ink #W1					Water-based Ink #W2					Water-based Ink #W3					Water-based Ink #W4				
	Blue	Green	White	Cyan	Mag-enta	Blue	Green	White	Cyan	Mag-enta	Blue	Green	White	Cyan	Mag-enta	Blue	Green	White	Cyan	Mag-enta
Acrylic acid polymers	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x
Alcohols	x	x	x	x				x				x	x	x	x	x	x	x	x	x
Amides or nitrogenous compounds	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x
Ethylene glycol ethers	x	x		x	x	x	x	x	x	x	x	x	x	x	x					
Hydrocarbons - high molecular weight	x	x				x	x	x		x						x	x	x	x	x
Hydrocarbons - low molecular weight						x	x			x										
Inorganics						x												x		
Olefin polymers											x	x	x	x	x					
Organic acids or salts			x	x	x						x	x	x	x	x					
Pigments - inorganic			x					x					x				x	x		
Pigments-organic		x			x	x	x			x	x	x					x			
Pigments-organometallic	x	x		x		x			x			x		x	x	x	x		x	x
Propylene glycol ethers														x	x	x			x	
Resins	x	x	x			x	x		x	x						x	x		x	
Siloxanes											x	x	x	x	x	x	x	x	x	x

Table 3.7 Categorization of Chemicals in UV-cured Inks Used in the Performance Demonstrations

Chemical category	UV-cured Ink #U1					UV-cured Ink #U2					UV-cured Ink #U3				
	Blue	Green	White	Cyan	Mag-enta	Blue	Green	White	Cyan	Mag-enta	Blue	Green	White	Cyan	Mag-enta
Acrylated polymers	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Acrylated polyols		x				x	x	x	x	x	x	x		x	x
Alcohols						x	x	x	x	x					
Amides or nitrogenous compounds	x	x	x	x	x						x	x	x	x	x
Aromatic esters	x	x	x	x	x						x	x	x	x	x
Aromatic ketones	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Olefin polymers	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Organophosphorous compounds			x					x					x		
Pigments - inorganic			x					x					x		
Pigments-organic	x					x	x				x				x
Pigments-organometallic		x		x	x	x	x		x	x		x		x	
Polyol derivatives						x	x		x	x					
Siloxanes	x	x	x	x	x						x	x	x	x	x

3.4 ENVIRONMENTAL AIR RELEASE ASSESSMENT

Releases to air result from the evaporation of chemicals during the flexographic printing process. This section of the chapter describes the methodology and results of the assessment of releases to air that can occur during makeready and production runs on a flexographic press. Releases to air are used to estimate inhalation exposure to particular chemicals for workers and the general population.

Two forms of air releases were examined: *stack* and *fugitive*. Stack emissions are collected from the press and are released through a roof vent or stack to the outside air, sometimes undergoing treatment to reduce the emissions. Fugitive emissions escape from the printing process (e.g., from a long web run between presses), and exit the facility through windows and doors.

Environmental Air Release Methodology

Air releases were calculated based on the amount of ink used and the weight percentages and vapor pressures of the ink components. Releases were estimated for the three types of ink (solvent-based, water-based, and UV-cured) and for each of the five colors (blue, green, white, cyan, and magenta). Figure 3.1 illustrates the overall mass balance, for which it is assumed that an equal amount of material enters and exits the system. The mass balance model does not take into account air releases from the use of cleaning solutions. For a detailed explanation of the method used to calculate the environmental releases and sample calculations, see Table 3-C.1 in Appendix 3-C.

Environmental Air Release Assumptions

The following assumptions were used to calculate environmental releases:

- Ink components with a vapor pressure greater than or equal to 0.001 millimeters of mercury (mmHg) at 25°C will volatilize.[6]
- 0.1% of the volatile components will be retained on the substrate.[7]
- 30% of the volatile compounds released to the air will be fugitive emissions, and 70% will be captured by the press system and released through a stack.[8]
- Solvent-based ink releases will pass through a catalytic oxidizer with a destruction efficiency of 95%.[9] There are no air pollution control devices for the water-based or UV-cured ink systems.
- Ink components that do not volatilize (those with a vapor pressure less than 0.001 mmHg at 25°C) will remain with the substrate, which ends up as product or is recycled.

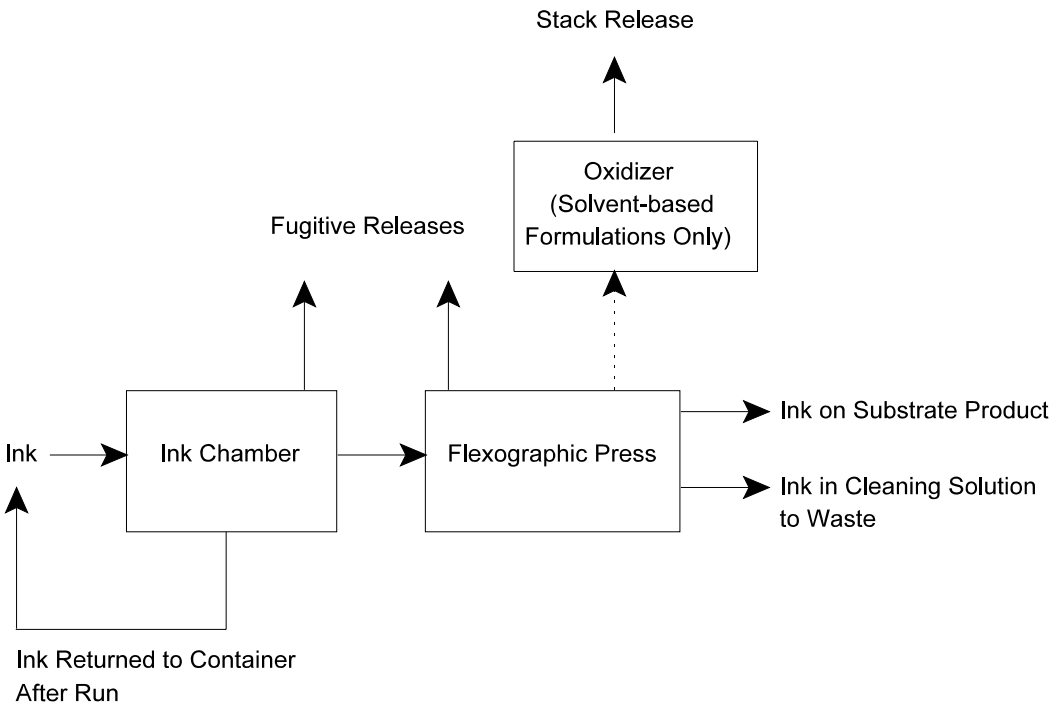

Figure 3.1 Mass Balance of Ink During Flexographic Printing

Environmental Air Release Limitations and Uncertainty

Uncertainties about the amounts of environmental releases relate to the rates of vapor generation, which vary depending on the following factors:

- speed of the printing press
- volatile content of the ink mixture
- equipment operating time
- temperature of the ambient air and ink system

In addition, release rates may vary depending on the capture efficiency of the press system and the destruction efficiency of the air control devices. If the capture or destruction efficiency increases, the release rate declines.

Environmental Air Release Results

Table 3-D.1 in Appendix 3-D presents the calculated environmental releases for each ink formulation. This table shows the total amount of chemicals volatilized, fugitive air releases, and stack air releases per press. Table 3.8, an excerpt from Table 3-D.1, presents environmental air release data for Solvent-based Ink #S2 at Site 10 and Water-based Ink #W2 at Site 1. Table 3.8 is included in the text to show the format of the data and to indicate the magnitude of air releases.

The calculated volatilization rates of the solvent-based inks were considerably higher than those for the other two ink systems. The total amount volatilized averaged 6.23 g/sec. The average stack emissions (0.216 g/sec) were considerably lower than fugitive emissions (1.87

g/sec), reflecting the anticipated use of oxidizers with stack emissions. Therefore, of the total amount volatilized, only a portion would ultimately be released to the atmosphere.

The volatilization rates for water-based inks were considerably lower than those for solvent-based inks, with an average rate of 0.347 g/sec. However, the stack releases, averaging 0.250 g/sec, were calculated to be higher than those for solvent-based inks, because the use of an oxidizer was not anticipated. On the other hand, the fugitive emissions, with an estimated average of 0.105 g/sec, were anticipated to be considerably lower than those for solvent-based inks, because of the lower average VOC content of water-based inks.

The UV-cured inks were calculated to have releases comparable to those of water-based inks, with a total volatilization rate of 0.438 g/sec. The estimated stack and fugitive releases were calculated to be 0.304 and 0.141 g/sec, respectively. These figures were calculated with the assumption that 100 percent of the volatile components of the inks would be released to the air. In reality, much of the volatile content would be incorporated into the coating during the UV curing process. The decrease in emissions under real-world conditions is unknown.

Air releases also varied among colors within each ink system; the differences are primarily due to different consumption rates. White ink had significantly higher emission and consumption rates than the other colors because it covered a greater percentage of the image area (see Table 6.1 in Chapter 6: Resource and Energy Conservation). Blue and green inks had slightly higher air releases and consumption rates than cyan and magenta inks.

Press speed also greatly affected the amount of ink consumed. All estimates were made assuming a press speed of 500 feet per minute (fpm) for all three ink systems. With this press speed, ink consumption rates were approximately the same for the different ink formulations. If the speeds observed during the performance demonstrations were used instead, however, a reduction in the ink consumption rate and environmental air releases would result. A reduction in UV-cured formulation press speed from 500 fpm to 340 fpm (a 32.0% reduction in press speed) would be expected to decrease the consumption rates and releases by approximately 32%. Similarly, reductions in press speed to 453 fpm and 394 fpm for solvent-based and water-based formulations, respectively, would be expected to cause reductions in ink consumption rates and environmental releases of 9% and 21%, respectively. Equipment specifics, such as the choice of anilox roll volume, also may affect ink consumption rates. In particular, UV-cured inks often require lower-volume anilox rolls than the other two ink systems because less UV-cured ink generally is needed per unit of printed area.

Adding solvents, reducers, extenders, cross-linkers, and other compounds to a printing ink usually increases its volatile content, resulting in greater environmental releases. During the CTSA performance demonstrations, solvents were added in greater quantities to the solvent-based formulations than to water-based or UV-cured formulations, which further increased releases from solvent-based inks.

Table 3.8 Sample Environmental Air Release Results [a]

Chemical category *(Press-side solvents and additives in italics)*	Blue			Green			White			Cyan			Magenta		
	Air releases per press (g/sec)														
	Total amount volati-lized	Amount of fugitive releases	Amount of stack releases	Total amount volati-lized	Amount of fugitive releases	Amount of stack releases	Total amount volati-lized	Amount of fugitive releases	Amount of stack releases	Total amount volati-lized	Amount of fugitive releases	Amount of stack releases	Total amount volati-lized	Amount of fugitive releases	Amount of stack releases
Solvent-based Ink #S2 – Site 10															
Alcohols	0.197	0.059	0.007	0.244	0.073	0.008	0.407	0.122	0.014	0.199	0.060	0.007	0.208	0.062	0.007
Alkyl acetates	0.126	0.038	0.004	0.125	0.038	0.004	0.142	0.043	0.005	0.154	0.046	0.005	0.062	0.019	0.002
Hydrocarbons - low molecular weight	0.074	0.022	0.003	0.102	0.030	0.004	0.334	0.100	0.012	0.060	0.018	0.002	0.137	0.041	0.005
Alcohols	0.045	0.013	0.002	0.047	0.014	0.002	0.069	0.021	0.002	0.042	0.013	0.001	0.075	0.023	0.003
Hydrocarbons - low molecular weight	0.004	0.001	0.000	0.003	0.001	0.000	0.014	0.004	0.000	0.004	0.001	0.000	0.005	0.001	0.000
Alcohols	0.603	0.181	0.021	0.659	0.198	0.023				0.345	0.104	0.012	0.792	0.238	0.028
Added: Propanol							*1.220*	*0.366*	*0.043*						
Added: Propylene glycol monomethyl ether										*0.315*	*0.095*	*0.011*	*0.069*	*0.021*	*0.002*
Added: 2-Methoxy-1-propanol										*0.006*	*0.002*	*0.000*	*0.001*	*0.000*	*0.000*
Water-based Ink #W2 – Site 1															
Amides or nitrogenous compounds	0.002	0.000	0.001	0.003	0.001	0.002	0.092	0.028	0.065				0.002	0.001	0.002
Hydrocarbons - high molecular weight	0.001	0.000	0.001	0.002	0.001	0.001	0.015	0.005	0.011				0.001	0.000	0.000
Hydrocarbons - low molecular weight	0.001	0.000	0.000	0.001	0.000	0.001									
Alcohols							0.038	0.011	0.027						
Ethylene glycol ethers							0.038	0.011	0.027						
Added: Isobutanol	*0.001*	*0.000*	*0.000*							*0.001*	*0.000*	*0.001*	*0.001*	*0.000*	*0.001*

3.5 OCCUPATIONAL EXPOSURE ASSESSMENT

This section describes the exposure assessment of flexographic printing plant workers to the chemicals in the flexographic ink formulations. An exposure assessment—the third step in a risk assessment—defines the expected exposures of an identified population to specific chemicals.

Two scenarios were studied for this exposure assessment: workers in the ink preparation room, and workers in the press room during a print run. Prior to a production run, the potential for exposure exists for workers transferring and mixing inks in the ink preparation room. During the production run, inhalation and dermal exposures can occur when workers handle ink cans and operate the press. Inhalation exposures were estimated using the EPA mass balance model; dermal exposures were estimated using an EPA dermal exposure model.

The exposure assessment indicates the relative exposure levels that result from each ink system. It can also indicate whether exposure results from primarily dermal or inhalation pathways, and therefore may indicate whether exposure reduction measures might be effective for a given ink system (e.g., if a facility requires the use of gloves, dermal exposure could be nearly eliminated). The two scenarios of the assessment can also assist in determining the variation of exposure depending on a worker's location in a printing facility.

Occupational Exposure Methodology

The occupational exposure assessment used a model facility approach, in which reasonable and consistent assumptions were used for each ink type. Data to characterize the model facility were aggregated from a number of sources, including flexographic printing facilities and industry suppliers in the United States. The model facility is not entirely representative of any existing facility. Thus, actual exposure (and risk) could vary substantially depending on site-specific operating conditions, end-products, age of pollution control equipment, and other factors.[d]

For a detailed explanation of the method used to calculate occupational exposures, see Appendix 3-E.

Exposure Scenarios

In Scenario I, workers were assumed to be exposed in the ink preparation room while pumping ink from a 55-gallon drum into five-gallon cans, and while mixing inks in the five-gallon cans. Under this scenario, one worker was assumed to be exposed for 48 minutes per formulation per shift.

In Scenario II, workers were assumed to be exposed to fugitive emissions released into the printing room air, both by operating the printing press for a 7.5-hour shift and by adjusting the inks in the five-gallon cans next to the ink press for 1-2.5 hours, depending on the ink

[d]Many facilities conduct exposure monitoring to measure worker exposure rates. If monitoring data are available, they can be used with other data in this analysis to determine whether facility-specific conditions pose a low, potential, or clear concern for risk according to the scale used in this study. To do this, a reader should compare exposure data to the hazard data reported in Appendix 3-B. By following the procedures outlined in Section 3.7 and Table 3.13, the reader can conduct a site-specific comparative risk assessment.

type. Scenario II used the printing room mass balance model to estimate exposures. The following assumptions were made:

- Only one source (ink can) within the work area emits the chemical.
- The concentrations of the chemicals in a mixture are constant throughout the time of dermal absorption.[12]
- The average surface area of two hands is 1,300 cm^2. After coming into contact with a chemical, the quantity of chemical remaining on the hands is assumed to be 1-3 mg/cm^2. Dermal exposure is modeled assuming that the worker has routine two-hand contact with the inks. Dermal exposures are based on an 8-hour, time-weighted average.[12]
- There are three shifts per day. Each worker works 7.5 hours per day and 250 days per year.
- A total of nine workers are exposed per shift; one worker exposed in Scenario I (one worker per shift) and eight workers exposed in Scenario II (two workers per press per shift, four presses).

Table 3.9 lists the general facility assumptions that were developed for both scenarios. See Appendix 3-E for a more detailed discussion of the model facility parameters.

Table 3.9 Occupational Exposure Methodology Assumptions

Assumption	Value	Source
Temperature of the ink during transfer	25°C	EPA[12]
Average ventilation rate in both rooms	7,000 ft^3/min	Average of Technical Committee responses
Ventilation/room air mixing factor	0.5	EPA[12]
Velocity of the air across the cans	100 fpm	EPA[12]
Press emissions capture rate	70%	Technical Committee response[a]
VOC destruction efficiency of oxidizer	95%	Technical Committee response
Diameter of the five-gallon cans	1 ft	EPA[12]
Press speed	500 fpm	Performance methodology
Exposure time in the ink preparation room	48 min/ formulation	Technical Committee response
Exposure time adjusting five-gallon ink can near the press — solvent-based inks	2.5 hr	Technical Committee response
Exposure time adjusting five-gallon ink can near the press — water-based inks	1.0 hr	Technical Committee response
Exposure time adjusting five-gallon ink can near the press — UV-cured inks	2.0 hr	Technical Committee response

[a]The capture rate for newer or retrofitted presses will be considerably higher (approximately 85%) due to the use of enclosed doctor blades.

Inhalation Exposure

The amount of a chemical in a room was calculated as follows:

Amount of chemical in a room = (the amount of chemical entering the room + the amount of chemical generated in the room – the amount of chemical leaving the room.)

This analysis used a different mass balance model for each scenario.

- Scenario I used an open surface mass balance model to estimate the volatilization of liquids from open surfaces. For chemicals with vapor pressures less than 35 mmHg at 25°C, one vapor generation rate was used.[10] For chemicals with vapor pressures greater than or equal to 35 mmHg at 25°C, a different vapor generation rate was used (see Appendix 3-E).[11]
- Scenario II used a printing room mass balance model to calculate chemical concentrations in the printing room based on fugitive emission and room ventilation rates.
- Inhalation exposures to components with a vapor pressure less than 0.001 mmHg at 25°C were assumed to be negligible.[6]

Dermal Exposure

Dermal exposures may result from contact with the inks during transferring and mixing of the inks both before and after the production runs. A dermal contact model provided upper and lower "bounding" estimates of dermal exposure. Because glove usage is not universal in the printing industry, the data were calculated based on the conditions for a worker who does not use gloves or barrier creams.[12] In situations where the ink formulation was corrosive, dermal exposure to workers was considered negligible, because it was assumed that workers wore gloves when working with corrosive chemicals.

Occupational Exposure Limitations and Uncertainty

Any determination of the occupational exposure levels associated with flexographic printing activities requires making assumptions about the printing process, the workplace environment, and health and safety practices. Occupational exposure levels differ among facilities because of many variables, including the following:

- procedures used in handling the ink formulations
- press speed
- capture efficiency of the press system
- equipment operating time
- temperature conditions (ambient and ink)
- volatility of the chemicals in the inks
- ventilation conditions and shop layout
- number of presses per facility
- use of personal protective equipment and safety procedures

Occupational Exposure Results

The results indicated that workers under Scenario I would have lower exposures than workers exposed in Scenario II. This difference was due to the shorter exposure time in the

ink preparation room, and to the lower vapor generation rates resulting from an open can of ink versus those resulting from fugitive emissions in the printing room.

The occupational exposure results indicated that dermal exposure was comparable in the ink preparation room (Scenario I) and the press room (Scenario II). However, inhalation exposure in the ink preparation room was very low compared to that in the press room. For this reason, only the results from Scenario II were used in the risk characterization. The results of both scenarios are presented in Appendix 3-F.

Tables 3-F.1 and 3-F.2 in Appendix 3-F present potential inhalation exposure rates, minimum dermal exposure rates, and maximum dermal exposure rates for both scenarios. Exposure rates are given for each chemical category in each of the five formulations for each of the nine product lines: the higher the value (in mg/day), the greater the exposure to that chemical via the given exposure pathway. The minimum and maximum dermal exposure rates provide a range for the dermal pathway. Press-side solvents and additives were incorporated into the data tables for Scenario II; therefore, Scenario II data were site-specific.

Table 3.10, an excerpt from Table 3-F.1, presents occupational exposure data for Solvent-based Ink #S2 at Site 10 (Scenario II). Table 3.10 is included in the text to show an example of the format of the data and to indicate the magnitude of occupational exposure.

As discussed in the environmental release section, solvent-based formulations exhibited higher volatilization rates and higher fugitive emissions. Solvent-based inks therefore created higher inhalation exposures than did water-based or UV-cured formulations. Water-based and UV-cured formulations resembled each other in levels of volatile emissions and worker inhalation exposures.

Ink consumption rates affected fugitive emissions and therefore affected occupational exposure levels. Because ink consumption rates varied by color, workers were exposed to the greatest amounts of volatile compounds from white inks. Also, the addition of solvents, reducers, extenders, cross-linkers, and other compounds to the printing inks resulted in greater occupational exposures.

Table 3.10 Sample Occupational Exposure Results, Scenario II (Press Room) [a]

Chemical category *(Press-side solvents and additives in italics)*	Blue			Green			White			Cyan			Magenta		
	Inhalation exposure (mg/day)	Dermal exposure (mg/day)		Inhalation exposure (mg/day)	Dermal exposure (mg/day)		Inhalation exposure (mg/day)	Dermal exposure (mg/day)		Inhalation exposure (mg/day)	Dermal exposure (mg/day)		Inhalation exposure (mg/day)	Dermal exposure (mg/day)	
		min.	max.		min.	max.		min.	max.		min.	max.		min.	max.
Solvent-based Ink #S2 – Site 10															
Alcohols	1,310	183	548	1,624	199	597	2,712	140	421	1,324	175	524	1,386	164	492
Alkyl acetates	838	117	350	835	102	307	945	49	147	1,028	135	406	415	49	147
Hydrocarbons - low molecular weight	494	69	206	677	83	249	2,223	115	345	401	53	159	911	108	323
Alcohols	297	41	124	312	38	115	457	24	71	279	37	110	502	59	178
Resins	0	183	550	0	175	525	0	188	565	0	171	514	0	105	316
Hydrocarbons - low molecular weight	25	4	11	18	2	6	95	5	15	25	3	10	32	4	11
Siloxanes	0	7	21	0	7	22	0	8	24	0	7	20	0	6	19
Amides or nitrogenous compounds	0	7	21	0	7	22	0	8	24	0	7	20	0	6	19
Organic acids or salts	0	7	21	0	7	22	0	8	24	0	7	20	0	6	19
Alcohols	4,019	560	1,681	4,387	537	1,612				2,301	303	910	5,274	624	1,871
Polyol derivatives	0	26	78	0	14	41				0	23	68	0	17	50
Amides or nitrogenous compounds	0	7	21	0	7	22				0	7	20	0	6	19
Organophosphorous compounds	0	7	21	0	7	22				0	7	20	0	6	19
Pigments - organometallic	0	53	158	0	13	39				0	84	251			
Pigments - inorganic				0	59	177	0	334	1,003						
Pigments - organometallic	0	29	88												
Pigments - organic				0	29	86									
Pigments - organometallic				0	13	38									
Pigments - inorganic													0	83	249
Added: Propanol							*8,128*	*420*	*1,261*						
Added: Propylene glycol methyl ether										*2,099*	*277*	*830*	*463*	*55*	*164*
Added: 2-Methoxy-1-propanol										*43*	*6*	*17*	*9*	*1*	*3*

[a] Shaded areas indicate where data are not applicable (i.e., the chemical category was not found in the particular formulation).

3.6 GENERAL POPULATION EXPOSURE ASSESSMENT

This section describes the exposure assessment of the general population living near a flexographic printing facility to the chemicals in the flexographic ink formulations. The general population is anyone not directly involved in the flexographic printing process who lives near a printing facility. These people may breathe air containing small amounts of vapors from evaporation of products at the facility.

The amount of exposure to these chemicals by the general population depends on several factors:

- distance from the facility
- the actual route of contact (e.g., inhalation)
- the length of time the chemical has been in the environment
- the way in which the chemical moves through the environment

Therefore, measuring internal facility contaminant levels may not be sufficient to determine significant general population exposure. Certain types of controls may move the chemical from inside the plant to the outdoors. It is also important to note that some chemicals may have a more significant impact on a specific segment of the general population, such as children, than on a typical worker.

Preliminary modeling was performed for both peak and average exposure. Short-term effects, such as eye irritation, are best predicted by peak exposure estimates, since the effect occurs within a short period of exposure. Long-term effects, such as carcinogenicity, are better predicted through average exposures because the effects depend on the cumulative exposure of an individual. The analysis also sought to determine whether the aggregate releases of facilities within a model region result in higher exposures for the general population compared to the releases from a single flexographic facility.

General Population Exposure Methodology

For this exposure assessment, it was assumed that fugitive and stack releases from a flexographic printing facility mixed with outside air. The resulting air concentrations depend on weather conditions. Stagnant conditions will not move vapors away quickly, so local concentrations of the chemical will be higher near the plant. Windy conditions will transport vapors away faster, thereby reducing local concentrations.

This assessment addressed acute and chronic exposure concerns for two exposure scenarios: local and regional. The local scenario considered a single facility in normal operation that has certain releases affecting a specific area and specific local population. The regional scenario considered the cumulative impact of all flexographic printing facilities within a region; in this case, Chicago, Illinois was used to model regional exposure. In both cases a model facility approach was used to calculate generic releases and environmental concentrations.

For the local exposure scenario, two models that were developed as regulatory models by the EPA's Office of Air and Radiation[15] were run to separately model the peak and average exposures. A short-term model, the Industrial Source Complex Short Term (ISCST) model, was initially used to calculate peak exposures in order to determine acute risk. A long-term model, the Industrial Source Complex Long Term (ISCLT) model, was used to determine average exposures and chronic risk. When results for the peak ISCST model were used to

develop acute risk values, the results indicated that there is an insignificant likelihood of acute effects within the general population from any of the three ink systems. Therefore, the final analysis only considers chronic risk, which was determined by calculating average exposure with the ISCLT model.

Local Exposure Methodology

A model facility was used to estimate local exposure by determining a chemical's air concentration at a specified distance from the printing facility. San Bernardino, California, was used for the model because the weather conditions there result in the highest average concentrations of pollutants around the model facility of any of the approximately 500 weather stations in the United States.[14] The average concentrations around San Bernardino are within an order of magnitude of concentrations expected anywhere else in the country. That is, if the San Bernardino average concentration were estimated as 10 $\mu g/m^3$, then the average concentration anywhere else in the country would be between 1 and 10 $\mu g/m^3$.

To determine the long-term, local, general population exposure, EPA's Office of Pollution Prevention and Toxics used an implementation of ISCLT in the Graphical Exposure Modeling System (GEMS).[16] Appendix 3-G presents the input parameters used in the model.

The air concentration at 100 meters from a facility is often assumed for exposure modeling, because this is close enough to the release site so that the concentration is conservatively high (concentrations usually lessen with distance), but far enough away that a residential population could reasonably be expected to be present. To obtain the concentration at 100 meters, a special polar grid was entered into the model. Distances from the facility of 100, 200, 300, 400, 500, and 1,000 meters were specified, forming concentric circles (i.e., rings) on the grid. These rings, along with compass points, were then used to define arc-shaped areas, or sectors. The air dispersion model took three calculations per sector to obtain average air concentrations of chemical vapors. Finally, the compass point with the highest cumulative (i.e., stack plus fugitive) concentration at 100 meters was used to determine general population exposure. The model indicates whether a person at this distance would be exposed, but offers no estimate of the number of people that would be exposed.

From the average concentration in the air, estimated inhalation exposures for an individual can be calculated in different ways, depending on the toxicity factor of the modeled chemical. For the flexographic ink chemicals, the toxicity factors indicated the need for Average Daily Dose (ADD) and Average Daily Concentration (ADC) estimates for use in non-cancer chronic risk calculations.

The formulas for ADD and ADC are as follows:

$$ADD\ (mg/kg\text{-}day) = [(C)(IR)(ED)(1\ mg/1000\ \mu g)]/[(BW)(AT)]$$

$$ADC\ (mg/m^3) = [(C)(ED)(mg/1000\mu g)]/(AT)$$

where

- C = chemical concentration in air from air dispersion modeling ($\mu g/m^3$)
- IR = inhalation rate (m^3/day)
- ED = exposure duration (days): for residential exposures, the average hours per day spent at the house multiplied by the average years of residency. This factor includes considerations for the average time spent inside, outside, and vacation away from the house.

BW = average body weight (kg)
AT = average time of exposure/residency (days)

Appendix 3-G demonstrates how the parameter values were calculated and presents their underlying assumptions and references.

Regional Exposure Methodology

The regional scenario provides insight into the overall impact of releases from all of the flexographic printing facilities in an area to that area's general population. This approach permits the estimation of the cumulative exposures resulting from all of the flexographic printers in an area. The total residential population exposed to flexographic ink chemicals was not available, because the locations of all the flexographic printing facilities across the country were not known.

The regional scenario was partially modeled using facilities located in the six-county metropolitan area around Chicago, Illinois, to provide an example of cumulative exposures. Within this area, the State of Illinois Environmental Protection Agency reported six companies with a total of 222 flexographic presses in a land area of 3,717 square miles. The 1995 population of the area was approximately 7,500,000.[17] The model assumed that all of these printers used the same printing formulation at the same time. The average concentration of pollutants for the Chicago area was then calculated using local weather data by means of the BOXMOD model, also implemented in GEMS.[16]

Although a region with many facilities of a given industry might have cumulative exposures greater than the local exposure estimate, that was not the case here. Instead, the relatively small number of flexographic printing facilities within the large land area meant that the regional exposure values were uniformly only half to a third of the exposure levels calculated at 100 meters from an isolated facility. Because the risks from the regional results were insignificant, complete regional modeling was deemed unnecessary, and separate results are not reported in this CTSA.

General Population Exposure Limitations and Uncertainty

There is no one value that can be used to describe exposure. Not only is uncertainty inherent in both the parameters and assumptions used in estimating exposure, but the effects possible within a population are variable. Sources of exposure uncertainty include the following:

- the accuracy with which the model facility used in the assessment characterizes an actual facility;
- estimated exposure levels from averaged data and modeling in the absence of measured, site-specific data;
- data limitations in the Environmental Air Release Assessment (the release values are inputs for the general population modeling);
- the accuracy with which the models and assumptions represent the situation being assessed, and the extent to which the models have been validated or verified; and
- parameter value uncertainty, including measurement error, sampling (or survey) error, parameter variability, and professional judgment.

EPA's *Guidelines for Exposure Assessment* document defines and describes how risk (or exposure) descriptors are used to provide information about the position of an exposure estimate in the distribution of possible outcomes.[18] One of four descriptors might be used, depending on the type and quality of data used in the analysis:

- central tendency
- high-end
- bounding
- what-if

In an ideal exposure analysis, all data would have both a value and some information about the associated probability distribution. If all data are based on average or median estimates, the analysis would be termed "central tendency," since it represents exposures that would typically be encountered. If all data are based on an exposure expected to be larger than that experienced by 90 percent of the population, the analysis is described as "high-end." An alternate descriptor is that the data represent "bounding" exposures; i.e., calculated exposures are higher than any expected actual exposures.

In some analyses, however, probability data are not available for each piece of information. In these cases, data are based on a set of circumstances (without indication of how probable that circumstance is). Such analyses are known as "what-if scenarios." Because, along with other factors, the probability of a flexographic facility being similar to that of our model facility could not be determined, the exposure analysis in this CTSA is considered a "what-if scenario."

General Population Exposure Results

Table 3-H.1 in Appendix 3-H presents fugitive and stack chemical concentrations 100 meters from the model facility for each chemical category and press-side solvent or additive. Table 3-H.2 in Appendix 3-H presents the Average Daily Dose (ADD) and Average Daily Concentration (ADC) for the general population (residential, 100 meters from the facility).

Tables 3.11 and 3.12, excerpts from Tables 3-H.1 and 3-H.2, present general population exposure data for Solvent-based Ink #S2 at Site 10. These tables are included in the text to show the format of the data and to indicate the magnitude of general population exposure.

General population exposure quantities depend on many of the same variables affecting environmental releases and occupational exposures. As a result, general population exposure results are affected in the same manner that environmental release and occupational exposure results are affected: by the volatility of the inks, ink consumption, press speed, and the use of press-side solvents and additives.

The general population exposure estimates show solvent-based inks as having the highest ADD/ADC values of the three ink systems. This indicates that the higher fugitive emissions from solvent-based inks outweigh the decrease in stack emissions resulting from the use of oxidizers on solvent-based presses. There is no clear difference between the ADD/ADC values of water-based and UV-cured inks, but they are both significantly lower than those for solvent-based inks.

Table 3.11 Sample General Population Exposure Results for Fugitive and Stack Concentrations [a]

Chemical category *(Press-side solvents and additives in italics)*	Blue		Green		White		Cyan		Magenta	
	Concentration (µg/m^3)									
	fugitive	stack	fugitive	stack	fugitive	stack	fugitive	stack	fugitive	stack
Solvent-based Ink #S2 – Site 10										
Alcohols	1.82e+01	2.27e-01	2.25e+01	2.81e-01	3.76e+01	4.70e-01	1.84e+01	2.30e-01	1.92e+01	2.40e-01
Alkyl acetates	1.16e+01	1.45e-01	1.16e+01	1.45e-01	1.31e+01	1.64e-01	1.43e+01	1.78e-01	5.77e+00	7.20e-02
Hydrocarbons - low molecular weight	6.92e+00	8.63e-02	9.49e+00	1.18e-01	3.12e+01	3.89e-01	5.62e+00	7.01e-02	1.28e+01	1.59e-01
Alcohols	4.17e+00	5.15e-02	4.37e+00	5.41e-02	6.41e+00	7.92e-02	3.91e+00	4.84e-02	7.03e+00	8.69e-02
Hydrocarbons - low molecular weight	3.50e-01	4.36e-03	2.45e-01	3.06e-03	1.31e+00	1.64e-02	3.52e-01	4.40e-03	4.49e-01	5.61e-03
Alcohols	5.64e+01	7.03e-01	6.15e+01	7.67e-01			3.23e+01	4.03e-01	7.40e+01	9.23e-01
Added: Propanol					*1.14e+02*	*1.42e+00*				
Added: Propylene glycol methyl ether							*2.91e+01*	*3.64e-01*	*6.43e+00*	*8.03e-02*
Added: 2-Methoxy-1-propanol							*5.95e-01*	*7.43e-03*	*1.31e-01*	*1.64e-03*

[a] Shaded areas indicate where data are not applicable.

Table 3.12 Sample General Population Exposure Results, Average Daily Dose (ADD), and Average Daily Concentration (ADC) [a, b]

Chemical category *(Press-side solvents and additives in italics)*	Blue		Green		White		Cyan		Magenta	
	ADD (mg/kg-d)	ADC (mg/m^3)	ADD (mg/kg-d)	ADC (mg/m^3)	ADD (mg/kg-d)	ADC (mg/m^3)	ADD (mg/kg-d)	ADC (mg/m^3)	ADD (mg/kg-d)	ADC (mg/m^3)
Solvent-based Ink #S2 – Site 10										
Alcohols	2.53e-03	1.34e-02	3.14e-03	1.66e-02	5.24e-03	2.78e-02	2.56e-03	1.36e-02	2.68e-03	1.42e-02
Alkyl acetates	1.62e-03	8.58e-03	1.61e-03	8.55e-03	1.82e-03	9.68e-03	1.98e-03	1.05e-02	8.02e-04	4.25e-03
Hydrocarbons - low molecular weight	9.62e-04	5.10e-03	1.32e-03	7.00e-03	4.33e-03	2.30e-02	7.82e-04	4.14e-03	1.78e-03	9.42e-03
Alcohols	5.79e-04	3.07e-03	6.08e-04	3.22e-03	8.91e-04	4.73e-03	5.44e-04	2.89e-03	9.78e-04	5.19e-03
Hydrocarbons - low molecular weight	4.86e-05	2.58e-04	3.41e-05	1.81e-04	1.83e-04	9.68e-04	4.90e-05	2.60e-04	6.25e-05	3.31e-04
Alcohols	7.84e-03	4.16e-02	8.55e-03	4.54e-02			4.49e-03	2.38e-02	1.03e-02	5.45e-02
Added: Propanol					*1.58e-02*	*8.40e-02*				
Added: Propylene glycol methyl ether							*4.05e-03*	*2.15e-02*	*8.94e-04*	*4.74e-03*
Added: 2-Methoxy-1-propanol							*8.27e-05*	*4.39e-04*	*1.82e-05*	*9.68e-05*

[a] Residential general population, 100 meters from the model facility
[b] Shaded areas indicate where data are not applicable.

3.7 RISK CHARACTERIZATION

Risk characterization integrates hazard and exposure information into quantitative and qualitative expressions of risk. This final step in a risk assessment enables experts to make a realistic estimate of risks to specific groups of people who are exposed to chemicals analyzed in earlier steps of the risk assessment. The accompanying text box describes how chemicals are grouped into categories of clear, potential, or low/negligible concern for risk.

Defining Risk Levels

Clear concern for risk indicates that for the chemical in question under the assumed exposure conditions, **adverse effects were predicted to occur.** A chemical was placed in this category if it had a Hazard Quotient (HQ) (see Note 1 below) greater than 10, or a Margin of Exposure (MOE) (see Note 2) equal to or less than 10 or 100 (depending on the type of available data). If the chemical did not have a HQ or MOE, but instead was analyzed by the structure activity team (SAT), the chemical was considered to be of clear concern for risk if it had a moderate or high hazard rating and exposure was predicted (see Note 3). Table 3.13 summarizes the HQ, MOE, and SAT criteria.

Potential concern for risk indicates that for the chemical in question under the assumed exposure conditions, **adverse effects may occur**. A chemical was designated as a potential concern for risk if it had a HQ between 1 and 10, or a MOE that either was between 10 and 100 or 100 and 1,000. A SAT-analyzed chemical was evaluated as a potential concern for risk if it posed a low-moderate hazard and exposure was predicted (see Note 3).

Low or negligible concern for risk indicates that for the chemical in question under the assumed exposure conditions, **no adverse effects were expected**. A chemical of low or negligible concern for risk had a HQ less than 1, or a MOE greater than 100 or 1,000. An SAT-analyzed chemical was evaluated as a low or negligible concern for risk if it had a low hazard rating (see Note 3).

Note 1. A Hazard Quotient (HQ) is the ratio of the average daily dose (ADD) to the Reference Dose (RfD) or Reference Concentration (RfC), where RfD and RfC are defined as the lowest daily human exposure that is likely to be without appreciable risk of non-cancer toxic effects during a lifetime. The more the HQ exceeds 1, the greater the level of concern. HQ values below 1 imply that adverse effects are not likely to occur.

Note 2. A Margin of Exposure (MOE) is calculated when a RfD or RfC is not available. It is the ratio of the NOAEL or LOAEL of a chemical to the estimated human dose or exposure level. The NOAEL is the level at which no significant adverse effects are observed. The LOAEL is the lowest concentration at which adverse effects are observed. The MOE indicates the magnitude by which the NOAEL or LOAEL exceeds the estimated human dose or exposure level. High MOE values (e.g., greater than 100 for a NOAEL-based MOE or greater than 1,000 for a LOAEL-based MOE) imply a low level of risk. As the MOE decreases, the level of risk increases.

Note 3. The Structure Activity Team (SAT) determined hazard levels based on analog data and/or structure activity considerations, in which characteristics of the chemicals were estimated in part based on similarities with chemicals that have been studied more thoroughly. SAT-based systemic toxicity concerns were ranked according to the following criteria:

- high concern — evidence of adverse effects in humans, or conclusive evidence of severe effects in animal studies
- moderate concern — suggestive evidence of toxic effects in animals; or close structural, functional, and/or mechanistic analogy to chemicals with known toxicity
- low concern — chemicals not meeting the above criteria.

Table 3.13 Criteria for Risk Levels

Level of concern	Hazard Quotient [a]	Margin of Exposure [b]		SAT Hazard Rating[e]
		NOAEL [c]	LOAEL [d]	
Clear risk	> 10	1 to 10	1 to 100	moderate or high
Potential risk	1 to 10	> 10 to 100	> 100 to 1,000	low-moderate
Low or negligible risk	< 1	> 100	> 1,000	low

[a] Hazard Quotient = ADD / RfD (RfC).
[b] Margin of Exposure = NOAEL (LOAEL) / Dose or Exposure Level.
[c] No Observed Adverse Effect Level.
[d] Lowest Observed Adverse Effect Level.
[e] This column presents the level of risk concern if exposure is expected. If exposure is not expected, the level of risk concern is assumed to be low or negligible.

Risk Characterization Limitations and Uncertainty

Estimated doses assume 100% absorption. The actual absorption rate, however, may be significantly lower, especially for dermal exposures to relatively polar compounds. This assessment used the most relevant toxicological potency factor available for the exposure under consideration.

Dermal exposure values to workers should be regarded as bounding estimates. The inhalation exposure estimates are "what-if" estimates.

Occupational Risk Results

Chemicals of Clear Concern for Risk

Categories with chemicals that present a clear concern for systemic and developmental risks to flexographic plant workers are shown in Tables 3.14 through 3.17. The type of exposure route (inhalation or dermal), the applicable formulation, and the chemical's function in the ink are listed for each formulation. For a presentation of the occupational risk data for systemic and developmental risks via dermal and inhalation pathways, see Appendices 3-I through 3-N.

The alcohols chemical category contained the most chemicals of clear concern for risk in the solvent-based and water-based ink formulations. Several amides or nitrogenous compounds in water-based ink formulations also presented a clear concern for systemic risks to workers. The acrylated polyols category contained many of the chemicals posing a clear concern for risk in the UV-cured formulations, based on toxicological data. Based on SAT reports, several other categories, including acrylated polymers and amides or nitrogenous compounds, contained chemicals that presented a clear concern for developmental effects.

Table 3.14 Clear Occupational Risk Concern: Chemical Categories for Solvent-based Inks #S1 and #S2 [a]

Exposure route	Type of risk	Categories with chemicals of clear concern [b, c]	Color	Function in ink
Solvent-based Ink #S1				
Inhalation	Systemic	Alcohols	All	Solvent
		Alkyl acetates	All but blue	Solvent
Dermal	Systemic	Alcohols	All	Solvent
		Alkyl acetates	Green, cyan, magenta	Solvent
		Inorganics	Magenta	Multiple Function
	Developmental	Alcohols	All	Solvent
		Inorganics	Magenta	Multiple Function
		Organic acids or salts (SAT)[d]	Blue	Additive
		Organometallic pigments (SAT)[d]	Blue, magenta	Colorant
		Organotitanium compounds (SAT)[d]	Blue, white	Additive
Solvent-based Ink #S2				
Inhalation	Systemic	Alcohols	All	Solvent
		Hydrocarbons — low molecular weight	All	Multiple Function
		Propylene glycol ethers	Cyan, magenta	Solvent
	Developmental	Alcohols	Blue	Solvent
Dermal	Systemic	Alcohols	All but white	Solvent
		Propylene glycol ethers	Cyan	Solvent
	Developmental	Alcohols	All	Solvent
		Organometallic pigments (SAT)[d]	Blue, magenta	Colorant

[a] Based on toxicological data, unless noted as an SAT-based concern.
[b] Criteria for clear risk concern are presented in Table 3.13.
[c] Each of these categories contains at least one chemical that was predicted to be of clear concern for risk.
[d] Developmental risks for SAT-evaluated chemicals were evaluated on a “concern/no concern” basis.

Table 3.15 Clear Occupational Risk Concern: Chemical Categories for Water-based Inks #W1 and #W2 [a]

Exposure route	Type of risk	Categories with chemicals of clear concern [b, c]	Color	Function in ink
Water-based Ink #W1				
Inhalation	Systemic	Alcohols	All but magenta	Solvent
		Amides or nitrogenous compounds	All	Multiple Function
		Ethylene glycol ethers	All but white	Solvent
Dermal	Systemic	Alcohols	All but magenta	Solvent
		Amides or nitrogenous compounds	All	Multiple Function
		Ethylene glycol ethers	All but white	Solvent
		Organic pigments	Magenta	Colorant
	Developmental	Alcohols	Blue, green	Solvent
Water-based Ink #W2				
Inhalation	Systemic	Alcohols	All but green	Solvent
		Amides or nitrogenous compounds	Green, white	Multiple Function
		Ethylene glycol ethers	All but green	Solvent
Dermal	Systemic	Alcohols	Blue	Solvent
		Amides or nitrogenous compounds	White, magenta	Multiple Function
		Ethylene glycol ethers (SAT)[d]	All	Solvent

[a] Based on toxicological data, unless noted as an SAT-based concern.
[b] Criteria for clear risk concern are presented in Table 3.13.
[c] Each of these categories contains at least one chemical that was predicted to be of clear concern for risk.
[d] Developmental risks for SAT-evaluated chemicals were evaluated on a “concern/no concern” basis.

Table 3.16 Clear Occupational Risk Concern: Chemical Categories for Water-based Inks #W3 and #W4 [a]

Exposure route	Type of risk	Categories with chemicals of clear concern [b, c]	Color	Function in ink
Water-based Ink #W3				
Inhalation	Systemic	Alcohols	All but cyan	Solvent
		Amides or nitrogenous compounds	All	Multiple Function
		Ethylene glycol ethers	Green	Solvent
Dermal	Systemic	Alcohols	Blue, green, white	Solvent
		Amides or nitrogenous compounds	All	Multiple Function
		Ethylene glycol ethers	Green	Solvent
		Organometallic pigments	Magenta	Colorant
	Developmental	Alcohols	All but cyan	Solvent
Water-based Ink #W4				
Inhalation	Systemic	Alcohols	All	Solvent
		Amides or nitrogenous compounds	All	Multiple Function
	Developmental	Amides or nitrogenous compounds	White	Multiple Function
Dermal	Systemic	Alcohols	All	Solvent
		Amides or nitrogenous compounds	Green, white	Multiple Function
		Organometallic pigments	Magenta	Colorant
	Developmental	Alcohols	All	Solvent
		Amides or nitrogenous compounds	Magenta	Multiple Function

[a] Based on toxicological data, unless noted as an SAT-based concern.
[b] Criteria for clear risk concern are presented in Table 3.13.
[c] Each of these categories contains at least one chemical that was predicted to be of clear concern for risk.

Table 3.17 Clear Occupational Risk Concern: Chemical Categories for UV-cured Inks #U1, #U2, and #U3 [a]

Exposure route	Type of risk	Categories with chemicals of clear concern [b, c]	Color	Function in ink
UV-cured Ink #U1				
Inhalation	Systemic	Acrylated polyols (SAT)	Green	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function
	Developmental	Amides or nitrogenous compounds (SAT)[d]	All	Multiple Function
Dermal	Systemic	Acrylated polyols (SAT)	Green	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function
		Organometallic pigments	Magenta	Colorant
	Developmental	Acrylated polymers (SAT)[d]	All	Oligomer
		Amides or nitrogenous compounds (SAT)[d]	All	Multiple Function
		Inorganic pigments (SAT)[d]	White	Colorant
UV-cured Ink #U2				
Inhalation	Systemic	Acrylated polyols	All	Monomer
	Developmental	Acrylated polyols	White	Monomer
Dermal	Systemic	Acrylated polymers	All	Oligomer
		Acrylated polyols	All	Monomer
		Organometallic pigments	Magenta	Colorant
		Organophosphorus compounds	White	Multiple Function
	Developmental	Acrylated polymers (SAT)[d]	All	Oligomer
UV-cured Ink #U3				
Inhalation	Systemic	Acrylated polyols (SAT)	All but white	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function
	Developmental	Acrylated polyols (SAT)	All but white	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function
Dermal	Systemic	Acrylated polyols (SAT)	All but white	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function
	Developmental	Acrylated polymers (SAT)[d]	All	Oligomer
		Acrylated polyols (SAT)[d]	All but white	Monomer
		Amides or nitrogenous compounds (SAT)[d]	All	Multiple Function

[a] Based on toxicological data, unless noted as an SAT-based concern.
[b] Criteria for clear risk concern are presented in Table 3.13.
[c] Each of these categories contains at least one chemical that was predicted to be of clear concern for risk.
[d] Developmental risks for SAT-evaluated chemicals were evaluated on a "concern/no concern" basis.

Most of chemicals presenting a clear occupational risk concern in solvent-based ink formulations are solvents; many chemicals presenting clear risk concern for water-based inks serve as solvents, colorants, and multi-function chemicals. For UV-cured ink formulations, most chemicals presenting a clear occupational risk concern serve as additives, monomers, oligomers, colorants, and the multiple function category.

Range of Occupational Risk Concern Levels by Chemical Category and Ink System

Table 3.18 summarizes the range of occupational risk concern levels (low concern, potential concern, or clear concern) for the three ink systems via dermal and inhalation routes. Because concern levels for systemic and developmental risk were very similar for each chemical category, the ranges for the two types of risk were combined. These ranges were based on toxicological data only, except for two chemical categories found in UV-cured inks: amides or nitrogenous compounds and aromatic esters, which had SAT data.

Each ink system contained chemicals with a clear concern for risk:

- Solvent-based inks had five chemical categories that contained chemicals of clear risk.
- Water-based inks had five chemical categories that contained chemicals of clear risk.
- UV-cured inks had four chemical categories that contained chemicals of clear risk.

Chemical categories within an ink system showed a wide variation in the level of risk concern. For example, ethylene glycol ethers in water-based inks ranged from low concern to clear concern. Variation also occurred among ink systems for certain chemical categories (e.g., certain alcohols in solvent- and water-based inks presented a clear concern, but alcohols in UV-cured inks presented a low concern). Such variations were due to differences in physical properties between chemicals in a category and/or differences in percent composition of an ink formulation.

Summary of Number of Chemicals of Clear Occupational Risk Concern by Product Line and Site

Table 3.19 summarizes of the number of chemicals that were found to be of concern for clear occupational risk. Solvent- and water-based ink product lines each included an average of 16 chemicals with clear risk concern (based on both toxicological and SAT-based data): an average of 29% for water-based inks, and 23% for solvent-based inks. Two of the three UV-cured inks had relatively few chemicals with clear concern; however, UV-cured Ink #U2 had 21 chemicals with clear concern (30%). It should be noted that these tallies do not necessarily give a full picture of risk concerns, because it is not possible to correlate the nature and severity of potential adverse effects on an aggregate product line level.

The total number of chemicals in an ink product line was determined by adding the numbers of base chemical ingredients and press-side solvents and additives for each formulation within a product line, and then summing the totals for all five formulations. Using this method, a chemical was counted more than once if it were found in more than one formulation. For example, ethanol, used in three formulations within a product line, was considered to be three "chemicals." However, if a chemical presented a clear risk concern for both dermal and inhalation pathways in a single formulation, it was counted only once. Similarly, if a chemical presented a clear risk concern for both systemic and developmental effects, it was counted only once.

Table 3.18 Range of Occupational Risk Concern (Combined Systemic and Developmental) [a, b, c]

Chemical category	Solvent-based	Water-based	UV-cured
Acrylated polymers			● ↔ ●●●
Acrylated polyols			● ↔ ●●●
Acrylic acid polymers		●	
Alcohols	● ↔ ●●●	● ↔ ●●●	●
Alkyl acetates	● ↔ ●●●		
Amides or nitrogenous compounds	●	● ↔ ●●●	moderate concern (SAT)
Aromatic esters	●		low to moderate concern (SAT)
Aromatic ketones			● ↔ ●●
Ethylene glycol ethers		● ↔ ●●●	
Hydrocarbons - high molecular weight	●	● ↔ ●●	
Hydrocarbons - low molecular weight	● ↔ ●●●	● ↔ ●●	
Inorganics	● ↔ ●●●	●	
Olefin polymers		●	●
Organic acids or salts	●	● ↔ ●●	
Organophosphorous compounds	● ↔ ●●		● ↔ ●●●
Organotitanium compounds	●		
Pigments - inorganic	● ↔ ●●	● ↔ ●●	● ↔ ●●
Pigments - organic	●	● ↔ ●●●	●
Pigments - organometallic	●	● ↔ ●●●	● ↔ ●●●
Polyol derivatives	●		●
Propylene glycol ethers	● ↔ ●●●	● ↔ ●●	
Resins	●	●	
Siloxanes	● ↔ ●●	● ↔ ●●	●

[a] The range of systemic and developmental risk concern levels were very similar for each chemical category and were therefore combined. The range of concern levels presented in this table represent the compounds in each chemical category that presented the lowest and highest risks for prep and press room workers from dermal and/or inhalation routes.

[b] Key: ● = low concern; ●● = potential concern; ●●● = clear concern

[c] Shaded areas indicate where data are not applicable.

Table 3.19 Summary of Number of Chemicals with Clear Occupational Risk Concern, by Product Line and Site

Ink type	Product Line	Site	Number of Chemicals[a]	Toxicological Data[a,b]		SAT Data[a,b]		Total Chemicals of Clear Risk Concern[a,b]		
				Number	Percent	Number	Percent	Number	Percent	Rank[c]
Solvent-based	#S1	9B	63	15	24%	2	3%	17	27%	5
	#S2	5	70	14	20%	0	0%	14	20%	10
		7	71	15	21%	0	0%	15	21%	9
		10	75	18	24%	0	0%	18	24%	7
Water-based	#W1	4	43	16	37%	0	0%	16	37%	1
	#W2	1	48	13	27%	3	6%	16	33%	2
	#W3	2	62	15	24%	0	0%	15	24%	6
		3	56	13	23%	0	0%	13	23%	8
	#W4	9A	66	18	27%	0	0%	18	27%	4
UV-cured	#U1	11	48	1	2%	6	13%	7	15%	12
	#U2	6	70	16	23%	5	7%	21	30%	3
	#U3	8	46	0	0%	9	20%	9	20%	11

[a] Chemicals are counted more than once if found in more than one formulation within the same product line. The number of chemicals may also include site-specific press-side solvents or additives.
[b] Includes clear concern for risk for systemic or developmental effects via inhalation or dermal routes.
[c] The ranking orders the product lines from the highest to lowest percentage of chemicals with clear concern for occupational risk.

Occupational Concern for Risk from Press-side Solvents and Additives

The use of additives increased the occupational risk for many of the solvent- and water-based ink formulations. In particular, propanol and propylene glycol methyl ether in solvent-based inks, and ammonia, propanol, isobutanol, and ethyl carbitol in water-based inks presented potential or clear occupational risk concerns in certain formulations. UV-cured inks typically do not use any press-side additives. In the performance demonstrations, however, one additive was used in UV-cured Ink #U2 (green).

Concern for Cancer Risk

Only a few ink formulations contained chemicals posing a concern for cancer. These included Water-based Ink #W1 (Site 4) and Water-based Ink #W2 (Site 1), which contained chemicals shown to produce tumors in rodents following dermal and/or inhalation exposures. An inorganic pigment found in every solvent-based, water-based, and UV-cured ink system is a possible carcinogen by the inhalation route of exposure. However, this compound, like other possibly carcinogenic compounds used in this project, does not pose significant risk because the exposure pathway for workers is different from that which results in carcinogenic effects.

General Population Risk Results

Categories with Chemicals of Potential General Population Concern for Risk

Categories with chemicals that present a potential risk concern for systemic and developmental effects in the general population are shown in Table 3.20. **No chemicals presented a clear concern for risk to the general population.** For a presentation of the general population risk data for systemic and developmental risks via inhalation, see Appendices 3-O and 3-P.

In the solvent-based and water-based ink product lines, alcohols found in Solvent-based Ink #S2, Water-based Ink #W2, and Water-based Ink #W3 were the only category with chemicals of potential general population risk concern based on toxicological data. (The alcohols served as solvents in these formulations.) For the UV product lines, acrylated polyols in UV-cured Ink #U2, serving as reactive diluents, were the only category with chemicals of potential risk concern based on toxicological data. Based on SAT reports, certain propylene glycol ethers in Solvent-based Ink #S2, amides or nitrogenous compounds in UV-cured Inks #U1 and #U3, and acrylated polyols in UV-cured Ink #U2 may present a risk to the general population.

Range of General Population Risk Concern Levels by Chemical Category and Ink System

Table 3.21 summarizes the range of general population risk levels for each of the three ink systems. The range of concern levels for systemic and developmental risk are very similar for each chemical category and were therefore combined in the table. These ranges are based on toxicological data only, except for two chemical categories in UV-cured inks: amides or nitrogenous compounds, and aromatic esters, which have SAT support.

Most of the chemicals presented a negligible concern for general population risk because the model anticipated little exposure to the general population in the model, and no chemicals presented a clear concern for risk. Each ink system had one category with chemicals that posed a potential risk concern for the general population: alcohols in solvent- and water-based inks, and acrylated polyols in UV-cured inks. Five additional categories in water-based inks, three in solvent-based inks, and one in UV-cured inks contained chemicals of low concern for risk to the general population.

Summary of Number of Chemicals of Potential General Population Risk Concern by Product Line and Site

Table 3.22 summarizes the number of chemicals with a potential risk concern for the general population, by product line and site. **Very few chemical categories include chemicals that carry a potential risk concern for the general population:** alcohols in Solvent-based Ink #2 (Site 5), Water-based Ink #W2 (Site 1), and Water-based Ink #W3 (Sites 2 and 3), and acrylated polyols in UV-cured Ink #U2 (Site 6). The number of chemicals in a product line was determined by the same method used for Table 3.19.

Table 3.20 Categories with Chemicals Having a Potential Systemic and Developmental Risk Concern for the General Population [a]

Exposure route	Type of risk	Chemical categories with potential risk [b]	Color	Function in ink
Solvent-based Ink #S1				
Inhalation	Systemic			
	Developmental			
Solvent-based Ink #S2				
Inhalation	Systemic	Alcohols	White, cyan, magenta	Solvent
	Developmental	Propylene glycol ethers (SAT)	Cyan, magenta	Solvent
Water-based Ink #W1				
Inhalation	Systemic			
	Developmental			
Water-based Ink #W2				
Inhalation	Systemic	Alcohols	White	Solvent
	Developmental			
Water-based Ink #W3				
Inhalation	Systemic	Alcohols	White	Solvent
	Developmental			
Water-based Ink #W4				
Inhalation	Systemic			
	Developmental			
UV-cured Ink #U1				
Inhalation	Systemic			
	Developmental	Amides or nitrogenous compounds (SAT)	All	Multiple Function
UV-cured Ink #U2				
Inhalation	Systemic	Acrylated polyols	White	Monomer
	Developmental			
UV-cured Ink #U3				
Inhalation	Systemic			
	Developmental	Acrylated polyols (SAT)	All but white	Monomer
		Amides or nitrogenous compounds (SAT)	All	Multiple Function

[a] Based on toxicological data, unless noted as an SAT-based concern.
[b] Criteria for potential concern for risk to the general population are presented in Table 3.13. No chemicals presented a clear concern for risk to the general population.

Table 3.21 Range of General Population Risk (Combined Systemic and Developmental) [a, b, c]

Chemical category	Solvent-based ink	Water-based ink	UV-cured ink
Acrylated polymers			❍
Acrylated polyols			❍ ↔ ●●
Acrylic acid polymers		❍	
Alcohols	● ↔ ●●	❍ ↔ ●●	❍
Alkyl acetates	●		
Amides or nitrogenous compounds	❍	●	moderate concern (SAT)
Aromatic esters	❍		low to moderate concern (SAT)
Aromatic ketones			❍ ↔ ●
Ethylene glycol ethers		❍ ↔ ●	
Hydrocarbons - high molecular weight	❍	●	
Hydrocarbons - low molecular weight	●	●	
Inorganics	❍	❍	
Olefin polymers		❍	❍
Organic acids or salts	❍	❍	
Organophosphorous compounds	❍		❍
Organotitanium compounds	❍		
Pigments - inorganic	❍	❍	❍
Pigments - organic	❍	❍	❍
Pigments - organometallic	❍	❍	❍
Polyol derivatives	❍		❍
Propylene glycol ethers	●	❍ ↔ ●	
Resins	❍	❍	
Siloxanes	❍	❍	❍

[a] The ranges of systemic and developmental risk concern levels were very similar for each chemical category and were therefore combined. The range of risk levels presented in this table represent the compounds in each chemical category that presented the lowest and highest risk concern for the general population via inhalation only.
[b] Key: ❍ = negligible concern because exposure is not anticipated; ● = low concern; ●● = potential concern; ●●● = clear concern
[c] Shaded areas indicate where data are not applicable.

Table 3.22 Summary of Number of Chemicals with Potential General Population Risk Concern, by Product Line and Site

Ink type	Product Line	Site	Number of Chemicals With Potential Risk Concern[a, b]	Number of Total Chemicals [b]	Percent
Solvent-based	#S1	9B	0	63	0%
	#S2	5	3	70	4%
		7	0	71	0%
		10	0	75	0%
Water-based	#W1	4	0	43	0%
	#W2	1	1	48	2%
	#W3	2	1	62	2%
		3	1	56	2%
	#W4	9A	0	66	0%
UV-cured	#U1	11	0	48	0%
	#U2	6	1	70	1%
	#U3	8	0	46	0%

[a] Includes potential risk concern for systemic or developmental effects via inhalation.
[b] Chemicals are counted more than once if found in more than one formulation within a product line. The number of chemicals includes site-specific press-side solvents and additives used in the performance demonstrations.

General Population Risk Concern from Press-Side Solvents and Additives

The use of press-side solvents and additives was found to increase the concern for risk to the general population for many of the solvent- and water-based inks formulations. In particular, propanol and propylene glycol ethers in solvent-based inks; and ammonia, propanol, isobutanol, and ethyl carbitol in water-based inks, presented low concern for risk to the general population in certain formulations.

Concern for Cancer Risk

Water-based ink #W2 (Site 1) contained one chemical that could expose the general population by the inhalation route; there is evidence of this chemical producing tumors in one species following inhalation exposure. Several of the carcinogenic chemicals identified were found to be of negligible general population risk concern, because incidental exposure of the general population to these chemicals was not expected.

REFERENCES

1. Cothern, C. Richard, William A. Coniglio, and William L. Marcus. "Estimating Risk to Human Health," *Environmental Science and Technology*. 20: 111-116, 1986.

2. Thayer, Ann M. "Alar Controversy Mirrors Differences in Risk Perceptions," *Chemical and Engineering News*. August 28, 1989, pp. 7-13.

3. U.S. Environmental Protection Agency (EPA). Not dated. "8e Submission Criteria for Determination of Level of Concern." Internal memorandum, Office of Pollution Prevention and Toxics.

4. Wagner, P.M., Nabholz, J.V., and Kent, R.J. "The New Chemicals Process at the Environmental Protection Agency (EPA): Structure-activity Relationships for Hazard Identification and Risk Assessment," *Toxicol. Lett*. 79: 67-73, 1995.

5. U.S. Environmental Protection Agency. Memorandum from Jennifer Seed to Terry O'Bryan entitled "Criteria for 8(e) CAP Submissions." March 25, 1994.

6. Reilly, B. "Memorandum from Breeda Reilly to CEB Staff: Guidance for Preparing PMN Engineering Reports." U.S. Environmental Protection Agency. June 4, 1994.

7. American National Can Company, anonymous source. Personal communication with James Rea, U.S. Environmental Protection Agency. Specific date unknown.

8. Warlick, Thomas, Graphic Packaging Corporation. Personal communication with James Rea, U.S. Environmental Protection Agency. November 20, 1997.

9. Serafano, John, Western Michigan University. Personal communication with James Rea, U.S. Environmental Protection Agency. 1997, specific date unknown.

10. Fehrenbacher, M.C. and A.A. Hummel. "Evaluation of the Mass Balance Model Used by EPA for Estimating Inhalation Exposure to New Chemical Substances," *American Industrial Hygiene Association*, submitted for publication.

11. Engel, A.J. and B. Reilly. *Evaporation of Pure Liquids from Open Surfaces*. U.S. Environmental Protection Agency, Pre-Publication Draft.

12. Chemical Engineering Branch, EPA. *Manual for the Preparation of Engineering Assessments*. U.S. Environmental Protection Agency. February 1991.

13. Brennan, Thomas. U.S. Environmental Protection Agency. Personal communication with Conrad Flessner, U.S. Environmental Protection Agency. February 1998.

14. General Sciences Corporation. *Exposure Screening Manual (Draft)*. Prepared for the U.S. Environmental Protection Agency. GSC-TR-32-88-015. May 10, 1988.

15. U.S. Environmental Protection Agency. *Industrial Source Complex (ISC2) User's Guide*. Research Triangle Park, NC: Environmental Protection Agency. EPA-450-4-92-008a. March 1992.

16. General Sciences Corporation. *Graphical Exposure Modeling System, GEMS, User's Guide,* 1991. GSC-TR-32-91-001.

17. Kaleel, Rob, State of Illinois Environmental Protection Agency. Personal communication with Conrad Flessner, U.S. Environmental Protection Agency. December 23, 1997.

18. U.S. Environmental Protection Agency. *Guidelines for Exposure Assessment*; *Notice*. Washington, DC: Environmental Protection Agency. Federal Register, pp. 22888-22938. May 29, 1992.